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VOLUME 40

1927

PUBLISHERS

AMERICAN MEDICAL ASSOCIATION

CHICAGO

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CARCINOMA OF THE PANCREAS^{*}

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Probably no other disease condition is more variable in its manifestations than carcinoma of the pancreas. The anatomic position of the organ, situated as it is in the center of the body cavity in such close relationship with so many important structures, makes tumor formation the origin of many striking and confusing syndromes. There are also symptoms and signs which are due to the impairment of the external and internal functions of the gland, as well as those which are referable to the cachexia and tissue necrosis of malignant disease in general.

In this paper the records of patients with cancer of the pancreas treated at the Peter Bent Brigham Hospital have been analyzed in order to establish, if possible, a definite clinical picture in which the various signs and symptoms can be evaluated, to aid in the diagnosis and treatment and to further a better understanding of the etiology, pathology and other broad aspects of the disease.

Of course, the perfect series of case records from the standpoint of an analysis made years after the records have been completed, does not exist, but I do not believe that there is available an appreciable number of case records of pancreatic carcinoma more detailed or complete in both positive and negative observations than those of the Peter Bent Brigham Hospital.

Because of the uncertainty of the diagnosis, only those cases in which the diagnosis has been verified by operative observation or at autopsy have been included in the series that is the basis of this paper. Practically all of the operative diagnoses were made by Dr John Homans and Dr David Cheever of the surgical staff of this hospital.

In all of the records of both the medical and the surgical services, I was able to find thirty-three proved cases of carcinoma of the pancreas, sixteen of which were certified by autopsy and seventeen by exploratory operation.

REVIEW OF THE LITERATURE

The literature on the subject is extensive and dates back to the first description of the condition by Mondiere¹ in 1836. Since then, several

^{*} From the Medical Service of the Peter Bent Brigham Hospital.

1 Mondiere, quoted by Parmentier and Chabral (footnote 11).

important papers have been written which have become classical in this subject. Among these are the papers of Da Costa ² in 1858, Ancelet ³ in 1864, Bard and Pic ⁴ in 1888, Mirallie ⁵ in 1893, Herringham ⁶ in 1894, Oser ⁷ in 1898 and Hulst ⁸ in 1905. Among the papers of more recent years are those of Fitcher ⁹ in 1919, Speed ¹⁰ in 1920 and Parmentier and Chabral ¹¹ in 1923. One of the outstanding points in the literature on the subject is the dearth of comprehensive works written in English. In most of the English systems of medicine the space allotted to pancreatic tumors amounts to only a few pages. The French apparently have been particularly interested in the subject.

Carcinoma of the pancreas seemingly seldom occurs in private practice, but in the large general hospitals it cannot be classed as a rare disease. Statistics show that it makes up an appreciable portion of the total number of cases of cancer. At the General Hospital in Vienna, there were twenty-two cases of cancer of the pancreas in 18,069 autopsies (Biach) ¹².

Segre found 127 cases in 11,472 postmortem examinations at Milan, Roswell Park ¹³ found 226 cases of primary carcinoma of the pancreas in 53,000 autopsies, Bashford ¹⁴ collected 1,000 cases from 84,448 autopsies. In 6,000 postmortem examinations at Guys Hospital, there were only twenty cases of primary malignant diseases of the pancreas, and in the first 1,500 autopsies at the Johns Hopkins Hospital there were only six cases ¹⁵. In this disease, as in any other condition, the incidence varies widely, this is due chiefly to the types of patients who are treated in the particular hospital. Comparison of these figures is of little value.

2 Da Costa, J. M. Cancer of the Pancreas, *N. Am. M. Chir. Rev.* **2** 883, 1858, *Tr. Path. Special Phil.*, 1860, vol. 1.

3 Ancelet, E. *Maladies du pancreas*, Paris, 1864, p. 53.

4 Bard, L., and Pic, Andrien. Cancer primitif du pancreas, *Rev. de med.* **8** 257 (April) 1888.

5 Mirallie, C. Cancer primitif du pancreas, *Gaz. d. hôp. Paris* **46** 889 (Aug. 19) 1893.

6 Herringham, W. P. Primary Cancer of the Pancreas, *St. Barth. Hosp. Rep.* **30** 5, 1894.

7 Oser, L. Carcinoma Pankreas, in Nothnagel, H. *Specielle Pathologie und Therapie* **18** 185, 1898.

8 Hulst, S. P. L. Zur Kenntnis der Genese des Adenokarzinoms und Karzinoms des Pankreas, *Virchows Arch. f. Path. Anat.* **180** 288 (May) 1905.

9 Fitcher, T. B. Cancer of the Pancreas, *Tr. A. Am. Phys.* **34** 284, 1919.

10 Speed, Kellogg. Carcinoma of the Pancreas, *Am. J. Med. Sc.* **160** 1 (July) 1920.

11 Parmentier, E., and Chabral, E. *Les tumeurs solides du pancreas*, *Nouveau traite de medicine* **15** 197, 1923.

12 Biach, quoted by Oser (footnote 7).

13 Park, Roswell, quoted by Mayo-Robson and Cammidge (footnote 16).

14 Bashford, quoted by McFarland (footnote 17).

15 Osler, W., and McCrea, Thomas. *The Principles and Practice of Medicine*, New York, 1923, ed. 9, p. 590.

for statistical purposes, because in some localities, such as Vienna, the primary and secondary growths are grouped with each other Mayo-Robson and Cammidge¹⁶ say that the reports made before 1900 are inaccurate because chronic interstitial pancreatitis causing occlusion of the common duct was not differentiated McFarland¹⁷ calls attention to the increase in the pathologic diagnosis of carcinoma of the pancreas at the expense of the diagnosis of primary cancer of the liver, simply because in many cases of malignant nodules in the liver, the more careful autopsies of recent years have disclosed a small primary growth embedded within the pancreas

About 1 or 2 per cent of the total number of cancers are found in the pancreas In 23,611 collected autopsies in Vienna, Biach found 2,005 cases of carcinoma, twenty-nine of which showed cancer in the pancreas either primary or secondary Eppinger¹² reported nineteen cases of pancreatic carcinoma in 308 cases of cancer found in 1,314 postmortem examinations

Futcher⁹ reported that of 41,949 patients admitted to the medical wards at the Johns Hopkins Hospital, a clinical diagnosis of carcinoma of the pancreas was made in fifty-eight cases, of 50,494 patients admitted to the medical and surgical wards of the Peter Bent Brigham Hospital, the diagnosis was made in fifty-nine cases In general, one may say that cancer of the pancreas is present in about 0.1 per cent of the patients admitted to general hospitals

Of all tumors of the pancreas, carcinoma is most common Other forms of tumors are comparatively rare Of the 132 pancreatic tumors reported by Segre,¹² 127 were cancer, two, sarcoma, two, cysts, and one was syphiloma Mayo-Robson and Cammidge state that new growths of the pancreas are common in dogs

REPORT OF CASES

The following are brief synopses of the symptoms, positive observations and results in the cases found in the records of the Peter Bent Brigham Hospital

CASE 1—M F, an Irishman, aged 60, was admitted to the hospital on July 1, 1913, with the complaint of jaundice His symptoms were a loss of 27 pounds (12.2 Kg) in weight beginning six months previous, anorexia and weakness for two months, jaundice and some nausea and vomiting for six weeks Jaundice was progressive, itching was moderate Epigastric distress and heartburn were present Examination showed an enlarged liver, a dilated gallbladder, a small, hard mass in the midepigastrium, edema of the legs and dry gangrene of the first and fourth toes of the left foot The blood pressure was systolic, 170, diastolic, 130 The temperature was 100 F Examination of the blood revealed erythro-

16 Mayo-Robson, A W, and Cammidge, P L The Pancreas, Its Surgery and Pathology, Philadelphia and London, 1907, p 512

17 McFarland, Joseph Surgical Pathology, Philadelphia, 1924, p 592

cytes, 3,300,000, hemoglobin, 55 per cent Occult blood was found in the stools and gastric contents Bile was absent in the stools

Cholecystostomy was performed on July 14 by Dr Cheever He reported "On incising the peritoneum there was a gush of several ounces of straw colored fluid The liver was enlarged, the gallbladder was thin and dilated, and the head of the pancreas was found to contain an irregular nodular mass in the region of common bile duct The mass was quite hard and about the size of a small hen's egg Glandular metastases were not made out, but on the upper surface of the left lobe of the liver there was a rounded elevation, about the size of a half dollar No other nodules were discovered in the liver The stomach, duodenum and transverse colon were normal" The patient died on July 22, 1913 Autopsy was not performed

CASE 2—H R, an American woman, aged 52, was admitted to the hospital on Aug 18, 1913, with the complaint of jaundice and vomiting The symptoms were a loss of 40 pounds (181 Kg) beginning about four months previously, progressive jaundice for three months, attacks of abdominal pain and vomiting for two and one-half months The vomitus consisted of large amounts of old food The pain, which began in the right upper quadrant and radiated to the midepigastrium, had become less severe The skin itched Examination showed a dilated stomach, enlarged liver and a small, deep mass in the midepigastrium The temperature was 99 F, the leukocyte count was 10,700, and free hydrochloric acid was present in the gastric contents The stools contained no bile or occult blood Cholecystostomy was performed on September 3 by Dr Homans The patient died on Sept 6, 1913 Autopsy was performed

The pathologic diagnosis was carcinoma of the pancreas, scirrhus type, with extension into surrounding tissue, compression but not occlusion of common bile duct, jaundice, laparotomy and cholecystostomy, interstitial pancreatitis, slight cirrhotic hepatitis, slight chronic diffuse nephropathy with acute degeneration, arteriosclerosis, chronic pleuritis, and chronic perihepatitis

CASE 3—F M, a Scotchman, aged 52, was admitted to the hospital on Aug 30, 1913, with the complaint of jaundice and pain in the lower part of the abdomen and back The symptoms were pain for five days following severe traumatic contusion of the lower part of the back and progressive jaundice for three days Anorexia, weakness and a burning sensation in the epigastrium developed after the patient was admitted to the hospital Examination showed an enlarged liver and dilated gallbladder The temperature varied from 99 to 103 F, the leukocyte count was from 14,000 to 34,000 The Wassermann test was positive, and there was no bile in the stools Death occurred on Sept 20, 1913 Autopsy was performed

The pathologic diagnoses were carcinoma of the duodenum (in anatomic situation of ampulla of Vater), carcinoma of the head of the pancreas, carcinoma of the peripancreatic, peribronchial, mediastinal and retroperitoneal lymph glands (metastatic), carcinoma of the liver (metastatic), carcinoma of the lung (metastatic), carcinoma of the pleurae (metastatic) visceral layers only, obstruction of the common bile duct (intraduodenal), carcinomatous distention of the extrahepatic bile passages and gallbladder, obstruction and distention of the pancreatic duct (intraduodenal), icterus, chronic pancreatitis, slight cirrhosis of the liver, chronic nephritis (slight), pleural adhesions (left), and peritoneal adhesions (localized)

CASE 4—G P, a Greek, aged 42, was admitted to the hospital on May 25, 1915, with the complaint of jaundice The symptoms were progressive jaundice, itching of the skin, loss of weight, weakness and anorexia of two months' duration—the order of appearance not being given He had a dull ache in the right hypochondrium Examination showed an enlarged liver and dilated superficial veins in the flanks The temperature was 99 F The leukocyte count was 8,000 and the hemoglobin 80 per cent No bile or blood was found in the stools Free hydrochloric acid was present in the contents of the stomach, and there was slight transient glycosuria Exploratory laparotomy was performed on June 9

by Dr Cheever The patient died on July 11 Autopsy was performed by Dr Stoddard The pathologic diagnoses were carcinoma of the pancreas (general), obstruction of the common bile duct, emaciation and ascites (slight)

CASE 5—A H, a Hungarian woman, aged 56, was admitted to the hospital on Sept 11, 1916, with the complaint of jaundice Her symptoms were a loss of 30 pounds (13.6 Kg) beginning eight weeks previously, jaundice for six weeks, progressive up to two weeks before admission, and itching Examination showed a distended gallbladder, a palpable but not much enlarged liver and an irregular firm mass in the midepigastrium The blood pressure was 170 systolic and 95 diastolic The temperature was 99 F The leukocyte count was 12,400, and the hemoglobin 75 per cent There was no bile in the stools The clinical diagnosis was carcinoma of the head of the pancreas

Cholecystenterostomy was performed on September 15 by Dr Homans, who reported "A very tense large gallbladder presented—there was a moderate sized, hard, slightly lobulated mass occupying the head of the pancreas fading off toward the left side of the abdomen and with an extension upward along the aorta toward the diaphragm The mass was about the size and shape of half the fist" The patient died on Jan 1, 1917 Autopsy was not performed

CASE 6—H G, a Russian, aged 62, was admitted to the hospital on Sept 11, 1917, with the complaint of jaundice and pain in the right groin The symptoms were progressive jaundice for two weeks, pain in the right groin for ten days, frequency and dysuria for eight days and constipation Examination showed jaundice, an enlarged liver and a distended gallbladder The temperature was 98 The leukocyte count was 5,800 and the hemoglobin 100 per cent There was no bile in the stools, and duodenal analysis showed no bile but the presence of pancreatic juice

Cholecystenterostomy was performed September 21 by Dr Homans He reported "A tense elongated gallbladder presented Behind the duodenum and extending from a point below corresponding to the head of the pancreas, upward and toward the median line at the level of the gastric artery was a stony hard, irregular mass, flattened and immovable, which gave the impression of carcinoma of the head of the pancreas It did not involve the duodenal wall but was evidently the cause of the shutting off of the common bile duct No gallstones were found" The patient died in April, 1918 Autopsy was not performed

CASE 7—C M, an American, aged 58, was admitted to the hospital on April 23, 1917, with the complaint of "rheumatism and stomach trouble" The symptoms were a loss of 20 pounds (9 Kg) beginning eight months previously, anorexia, numbness of the legs with swelling of the left leg for three months, gaseous eructations, nausea, vomiting and a dull, continuous pain in the epigastrium for two months Examination showed ascites, edema of the legs, weak heart sounds and an enlarged liver with an irregular border The temperature was 98 F, the pulse rate 110 Laboratory examination revealed an erythrocyte count of 3,900,000, a leukocyte count of from 18,000 to 24,000, and hemoglobin, 60 per cent The Wassermann reaction was positive There was mild but persistent glycosuria and achlorhydria The clinical diagnosis was scirrhus of the liver Death occurred on May 1, 1917 Autopsy was performed by Dr Marlow

The pathologic diagnoses were carcinoma of the pancreas (generalized) with metastases to the lungs, liver, peritoneum, epididymis, mesentery, retroperitoneal lymph nodes and suprarenals, chronic fibrous pleuritis, ascites, and obturator bands in the heart

CASE 8—B W, an Irish woman, aged 50, was admitted to the hospital on Sept 8, 1917, with the complaint of "pain in the stomach" Her symptoms were severe sharp pain just to the left of the upper sternum beginning six weeks previously and lasting for one week She then had pain beneath the right breast, anorexia for four weeks, nausea, vomiting and gaseous eructations for three weeks, epigastric pain for two weeks brought on by stooping, jaundice, and pain in the lower part of the back and in the left upper quadrant for one week Examination showed moderate jaundice, a palpable liver and a blood pressure of

185 systolic and 110 diastolic. The temperature was 98.6 F. The leukocyte count was 10,000, the erythrocyte count 5,700,000, and the hemoglobin 80 per cent, no bile was found in the stools, clinical diagnosis was cholelithiasis. Cholecystectomy and choledochostomy were performed on September 20 by Dr. Homans. He reported: "The gallbladder presented a deep bluish color, slightly distended and thickened. Exploration of the common duct was negative. There was nothing felt in the gallbladder or cystic duct. The head of the pancreas was markedly thickened, unusually firm but not stony hard. The common duct was opened and a sound was passed freely into the duodenum. The gallbladder was removed and the common duct drained." The wound continued to drain bile and the patient's symptoms were unrelieved. Exploratory laparotomy was performed November 19 by Dr. Homans. "On the surface of the liver were seen a number of yellowish white raised nodules principally on the inferior surface but there was one on the front which was excised. Immediate pathologic examination showed adenocarcinoma. A hard mass characteristic of cancer was felt in the posterior abdominal wall evidently carcinoma of the pancreas." The patient died before March 8, 1918. Autopsy was not performed.

CASE 9—F. E. M., an American woman, aged 46, was admitted to the hospital on Dec. 28, 1917, with the complaint of nausea and pain in the right upper quadrant. Her mother had died of diabetes. Since the age of 15 she had had periods of gnawing epigastric pain. The present symptoms were attacks of pain in the midepigastrium radiating to the left side of the back and associated with vomiting for the last year, constant nausea for eight weeks, loss of 12 pounds (5.4 Kg.) in eight months, anorexia and weakness for six weeks. Examination showed tenderness in the midepigastrium and an enlarged liver with a nodular edge. Roentgen-ray examination showed a deformed duodenal cap. The temperature was from 99 to 102 F. Laboratory examination showed leukocyte count, 5,300, hemoglobin, 90 per cent, bile found in the stools and normal gastric acidity. Exploratory laparotomy was performed on Jan. 4, 1918, by Dr. Homans. "There was a little free fluid. In the right lobe of the liver were seen a few whitish, raised, hard areas characteristic of metastatic carcinoma. Some of these were bluish in the center. They were somewhat thickly studded throughout the left lobe. Examination of the stomach was negative. The beginning of the duodenum was a little thickened and discolored and large dilated veins were noted. Behind the duodenum and pyloric region was an irregular, stony hard mass about the size of the palm of one's hand, apparently carcinoma of the pancreas. This appears to have partly involved the duodenal wall. There is, however, no obstruction of the common duct which is not dilated, and the gallbladder, although large, is fairly easily emptied. There is no evidence of malignant disease elsewhere in the abdomen or pelvis." The patient died on Feb. 14, 1919. Autopsy was not performed.

CASE 10—F. C. J., an American, aged 72, was admitted to the hospital on Jan. 4, 1918, with the complaint of dull pain in the right side of the abdomen and back. His symptoms were a loss of 30 pounds (13.6 Kg.) of weight, weakness, anorexia for five months and a dull ache in the right lower quadrant radiating to the lower part of the back for three months. Examination showed moderate emaciation, an enlarged liver and an irregular hard mass in the midepigastrium. Roentgen-ray examination showed deformity of the duodenum with spasm. The temperature was 99 F. The leukocyte count was 12,000, hemoglobin, 75 per cent, and achlorhydria was evident. The clinical diagnosis was carcinoma, the location of which was unknown. Exploratory laparotomy was performed on January 10 by Dr. Homans. "Examination showed a hard, very slightly lobulated mass, moving slightly with respiration and having in general the outlines of the head of the pancreas. This mass must have been several inches thick in the anterior-posterior direction, and the duodenum was pushed upward by it, making a long curve. The mass was retroperitoneal, and on the surface of it could be felt one or two fixed hard lymph glands. The gallbladder was full, large and slightly tense but could be partly emptied by pressure. No metastases were seen in the

liver, which was not enlarged Examination of the intestines and colon was negative Apparently the carcinoma was primary in the pancreas" Death occurred on Feb 22, 1918 Autopsy was not performed

CASE 11—E H N, a Canadian woman, aged 52, was admitted to the hospital on Aug 2, 1917, with the complaint of jaundice and weakness Nineteen years before she had had a hysterectomy performed for adenocarcinoma of the uterus Her symptoms were anemia and loss of 30 pounds (13.6 Kg) for ten months, extreme weakness for two months and jaundice for eight weeks She also had gaseous eructations and occasionally vomited The jaundice had possibly been diminishing for two weeks Two days previously she had bled profusely from the rectum Examination showed marked jaundice, an enlarged liver and slight edema of the legs Roentgen-ray examination showed the gallbladder with shadows suggesting stones The temperature was 100 F the pulse rate, 100 The leukocyte count was 7,200, the erythrocyte count, 2,900,000, and hemoglobin, 66 per cent There was no bile or occult blood in the stools Cholecystectomy and choledochostomy were performed on August 4 by Dr Cheever "Examination of the stomach and pylorus proved negative The gallbladder was shrunken thick walled, opaque and adherent to the duodenum Calculi were palpated within it Palpation revealed a rounded, somewhat irregular mass of varying consistency but nowhere very hard, lying behind the duodenum and pushing it forward This corresponded exactly to the head of the pancreas No stones were found in the common duct, which was dilated but a number 20 French bougie could be passed into the duodenum The gallbladder was removed and the common duct drained The diagnosis was cholelithiasis and chronic pancreatitis" The wound drained bile for eight weeks, and no bile appeared in the stools The patient's symptoms, except for the jaundice, were unrelieved Death occurred on March 10, 1918 Autopsy was performed by Dr Wolbach

The pathologic diagnoses were carcinoma of the duodenum with lymph node metastases and extension into the pancreas, biliary obstruction with great distention of the common and hepatic ducts, pancreatic obstruction with dilatation of the pancreatic duct, jaundice, absence of the gallbladder, surgical, absence of ovaries, tubes, and uterus, surgical, and of long standing tuberculosis in the lungs

CASE 12—C E, a Canadian woman, aged 70, was admitted to the hospital on Aug 6, 1918, with the complaint of jaundice The symptoms were a loss of 40 pounds (18.1 Kg) beginning ten weeks previously, progressive jaundice and abdominal disturbances for eight weeks and gradual loss of strength Examination showed marked jaundice, an enlarged liver and a distended gallbladder The temperature was 98 F The leukocyte count was 5,000, hemoglobin, 80 per cent The clinical diagnosis was obstructive jaundice due to malignant growth Cholecystenterostomy was performed August 15 by Dr Cheever "The liver was large, dark brown and firm and the gallbladder was immensely distended The stomach and pylorus were normal except for immensely distended veins in the pyloric region No nodules were noted in the liver and no glands were felt Exploration showed a hard cicatricial mass involving the gastrohepatic omentum especially marked at about the point where the cystic duct joins the common duct It appeared to be carcinoma of the ducts This communicated with a much larger mass lying more posteriorly and mesially, firm and nodular, which was either malignant disease of the upper part of the head of the pancreas or a mass of retroperitoneal glands The portion of the pancreas joining the second part of the duodenum did not appear to be affected, and my impression is that this was a primary carcinoma of the bile ducts No calculi were found" The patient died on Dec 28, 1918 Autopsy was not performed

CASE 13—J H, a Scotchman, aged 72, was admitted to the hospital on Aug 19, 1919, with a complaint of jaundice and gastric distress His symptoms were gaseous eructation, nausea and abdominal distress for six weeks, constipation and progressive jaundice for three weeks Examination showed marked

jaundice, a slightly enlarged liver, a temperature of 99 F, leukocyte count, 8,200, red cells, 3,500,000, hemoglobin, 55 per cent. Neither bile nor occult blood was present in the stools, but there was excess fat. A series of roentgenograms of the gastro-intestinal tract was negative. There was no achlorhydria. Cholecystoduodenostomy was performed on August 28 by Dr. Homans. "The gall-bladder was about the size of a lemon and very tense. The common duct was enlarged and in the region of the head of the pancreas, particularly behind the duodenum, was felt a stony hard, slightly irregular mass, which was slightly movable. There was an extension upward from it behind the common duct, presumably due to a chain of metastatic glands. Studded about the liver, especially on its inferior surface, were a number of small, yellowish nodules, some of which were umbilicated, evidently metastatic carcinoma. The pylorus was not distended or obstructed. A nodule on the anterior surface of right lobe of liver was excised." The patient died on Sept. 17, 1919. The pathologic diagnosis of the nodule was adenocarcinoma.

CASE 14—L. K., a Greek, aged 33, was admitted to the hospital on Sept. 23, 1919, with the complaint of anemia and weakness. His symptoms were a loss of 30 pounds (13.6 Kg.) during the last three years, anemia, weakness, severe constipation and an occasional substernal pain of three months' duration. He also had vertigo and some edema of the feet. Examination showed emaciation, no jaundice but a lemon yellow tint of skin and an irregular hard mass in the right epigastrium which moved with inspiration. The blood pressure was 98 systolic and 60 diastolic. The temperature was 98 F. There were 8,000 leukocytes and 2,088,000 erythrocytes, and a smear showed secondary anemia. Roentgen-ray examination showed obstruction at the beginning of the transverse colon and an irregularity in the outline of the stomach. Clinical diagnosis was carcinoma of the stomach. Exploratory laparotomy was performed October 9, by Dr. Homans. Death occurred on Oct. 30, 1919. Autopsy was performed by Dr. Wolbach.

The pathologic diagnoses were carcinoma of the head of pancreas involving the stomach and duodenum, metastases to the liver and regional lymph nodes, invasion of the portal vein and inferior vena cava by tumor, fatty myocarditis, congenital anomaly of the spleen and mesenteric attachments, passive congestion of the spleen and simple cyst of the kidney, left inguinal hernia. Microscopic examination showed the growth to be an adenocarcinoma of the pancreas.

CASE 15—O. A. S., a German, aged 75, was admitted to the hospital on Nov. 1, 1919, with the complaint of jaundice. His symptoms were a loss of 41 pounds (18.6 Kg.) beginning six weeks previously, epigastric distress, anorexia and progressive jaundice for six weeks, extreme weakness and swelling of the abdomen and legs for two weeks. Examination showed marked jaundice and emaciation, marked ascites and edema of the legs and abdominal wall and an enlarged, nodular, nontender liver. The temperature was 97 F. The leukocyte count was 12,500, the erythrocyte count 3,400,000, and hemoglobin, 70 per cent. The blood pressure was 105 systolic and 60 diastolic. Occult blood was present in the stools, but bile was absent. The clinical diagnosis was carcinoma involving the liver. Death occurred on Nov. 9, 1919. Autopsy was performed by Dr. Wolbach.

The pathological diagnoses were carcinoma of the tail of the pancreas with metastases to the liver, lungs and diaphragm, complete occlusion of the hepatic duct by tumor invasion, occlusion of the splenic vein and branches of the portal and hepatic veins by tumor invasion, hydrothorax, ascites, edema of the lower extremities, acute pericarditis, peritonitis, appendicitis, edema and congestion of the lungs, and jaundice.

CASE 16—W. E. D., an American, aged 50, was admitted to the hospital on Oct. 11, 1919, with the complaint of "intestinal trouble." His symptoms were loss of 50 pounds (22.7 Kg.) beginning three months previously, attacks of sharp, severe pain beginning in the left side and radiating to the front of the chest and to the abdomen for nine weeks and extreme weakness for six weeks. He did not

know that he was jaundiced. Examination showed marked emaciation and jaundice, widening of the aortic dulness, an enlarged liver and a distended gallbladder. The blood pressure was 104 systolic and 64 diastolic. The temperature was from 98.6 to 99.6 F., the pulse rate was 100. The erythrocyte count was 3,500,000, hemoglobin, 80 per cent, the leukocyte count, from 14,800 to 19,000. The Wassermann reaction was positive. Stools showed occult blood but no bile. Roentgen-ray examination showed diffuse increased density of the upper left lung and a shadow thought to be an aneurysm. Bismuth series were negative. The clinical diagnosis was carcinoma of the pancreas, syphilitic aneurysm and hepatitis. Death occurred on Nov 15, 1919. Autopsy was performed by Dr Adams.

The pathological diagnoses were carcinoma of the head of the pancreas, metastatic carcinoma of the liver, lungs, suprarenals and brain, obstruction of the common bile duct with dilatation of the common duct, gallbladder, hepatic, cystic and intrahepatic ducts, obstruction by lung metastasis of the upper branch of the left pulmonary artery with the accompanying vein beyond the bronchus, jaundice, bronchopneumonia, chronic fibrous pleuritis, ptosis of the transverse colon, arteriosclerosis, softening of the cerebrum, bilateral, and of the cerebellum, left.

CASE 17—J L S, a Scotchman, aged 55, was admitted to the hospital on Sept 2, 1920, with the complaint of abdominal pain and constipation. His symptoms were a loss of 15 pounds (6.8 Kg.), anorexia, abdominal distress and severe constipation of seven weeks' duration. The abdominal distress had increased to nocturnal attacks of severe, excruciating epigastric pain radiating to the lumbar spine. Examination showed slight emaciation and a rounded, firm mass in the left epigastrium 3 cm above the umbilicus and lying transversely, moving only slightly with respiration. The temperature was 98 F. Laboratory examination revealed leukocyte count, 7,400, hemoglobin, 90 per cent, no occult blood or excess fat in the stools and no achlorhydria. Tests with a bismuth series and barium enema were negative. The clinical diagnosis was carcinoma of the body of the pancreas. Exploratory laparotomy was performed on Oct 26, 1920, by Dr Homans. He reported "No free fluid. Stomach normal, large intestine normal, nothing felt on exploration of abdominal cavity except a stony hard, thick, immovable mass in the position of the pancreas, which could be best felt through the gastrohepatic omentum, tapering off toward the left but extending across the midline to the right and fading off in this direction. The mass was an inch in thickness at its thickest point, and lay practically over the aorta, and the great vessels of the small intestine ran through it. A small piece of the hardest part was excised, but I was afraid to go deep on account of the danger of injuring the mesenteric vessels. The specimen removed felt like scar tissue and may not be deep enough to show the lesion. The diagnosis was carcinoma of the pancreas." The pathologic report was chronic pancreatitis. Death, which occurred on Feb 6, 1921, was reported as due to cancer.

CASE 18—L J H, an American woman, aged 69, was admitted to the hospital on Jan 19, 1920, with the complaint of pain in the abdomen. Eight months previously she had undergone cholecystectomy for gallstones following typical symptoms of twelve years' duration. Stones were removed from the common duct with the gallbladder. The stomach and head of the pancreas were normal to palpation. Her symptoms were epigastric distress and heartburn for seven months, severe, dull, constant, epigastric pain radiating through to the left lumbar region of four months' duration, which was worse when the patient was lying down and was relieved when she was sitting up, nausea and vomiting for three weeks and jaundice for two days. She denied loss of weight, but her appearance indicated that she was losing weight. Examination showed moderate emaciation and jaundice. The blood pressure was 200 systolic and 94 diastolic. The temperature was from 98 to 100 F. The leukocyte count was 8,200 and hemoglobin 80 per cent. Bile was absent in the stools. Bismuth studies eight weeks previously had shown some ptosis of the stomach with a rather large six hour

residue, otherwise they were negative. The clinical diagnosis was carcinoma of the head of the pancreas. Exploratory laparotomy was performed on January 21 by Dr Cheever, who made the following observations: "A portion of the head of the pancreas just at the upper limit of the duodenum presented a hard nodular mass evidently involving the common duct, aggregating the size of an English walnut. The proximal common duct was markedly dilated. There were no metastases noted in the liver or glands. The duodenum was opened and a probe was passed into the papilla and up the common duct a short distance before meeting definite obstruction. The probe passed easily into the pancreatic duct, and there was a large amount of pancreatic juice but no bile. The ampulla was opened, but no calculi were found by passing a curet into the common duct. The diagnosis was carcinoma of the head of the pancreas." Death occurred on June 20, 1920. Autopsy was not performed.

CASE 19—M C, an American woman, aged 43, was admitted to the hospital on March 22, 1920, with the complaint of swollen glands on the left side of the face and neck. Her symptoms were a swelling of the preauricular, anterior and posterior cervical and the supraclavicular glands on the left side, of four months' duration, pain in the left side of the face and in the arm for one month, dryness of the mouth and marked generalized weakness for two weeks and profuse hematuria for one week. She had lost some weight. Examination showed marked pallor, a left facial paralysis with numbness of the left side of the face and tenderness in the left costovertebral angle. The temperature varied from 99 to 101 F, the pulse rate was 130 and the respirations, 26. The erythrocyte count was 2,300,000, hemoglobin, 40 per cent, the leukocyte count, 24,000, and polymorphonuclears, 80 per cent. Cystoscopy showed pointing of the left ureteral orifice and no apparent function on that side. The clinical diagnosis was renal tumor. Death occurred on April 6, 1920. Autopsy was performed by Dr Adams.

The pathologic diagnoses were carcinoma of the pancreas (generalized), generalized carcinomatosis, chronic passive congestion of the liver and kidneys, acute hemorrhagic pyelitis (bilateral), edema of the lungs and fatty degeneration of the heart.

CASE 20—F P F, an American, aged 65, was admitted to the hospital on Feb 2, 1921, with the complaint of pain in the abdomen. One brother had died of cancer. A few months previously he had undergone prostatectomy for retention of urine. His symptoms were a loss of 50 pounds (22.7 Kg) beginning three and one-half months previously, gas distress and a heavy dull ache in the region of the umbilicus radiating through to the back. The pain was worse when the patient lay on his right side. He had not noticed that he had jaundice. Examination showed slight emaciation, moderate jaundice and a mass in the mid-epigastrium. The temperature varied from 97 to 100.4 F. The leukocyte count ranged from 15,200 to 35,000. Bile and occult blood were present in the stools. The patient became extremely weak, and his left leg became edematous. Death occurred on Feb 15, 1921. Autopsy was performed by Dr Jacobson and Dr Wolbach.

The pathologic diagnoses were carcinoma of the pancreas (head) with metastases to the liver and regional lymph nodes, jaundice, infarction of the right lung (lower lobe), gallstone in the diverticulum of the gallbladder, chylous cysts of the ileum, chronic prostatitis, chronic epididymitis, infarct in the right kidney, hemorrhoids, cystitis cystica, thrombosis of the pulmonary artery, left iliac vein and prostatic plexus, and operative scars of the abdomen with hernia through the muscle in the right flank.

CASE 21—E W K, an American, aged 57, was admitted to the hospital on Dec 30, 1921, with the complaint of pain in the abdomen and weakness. His symptoms were occasional attacks of vomiting and marked progressive weakness for one year, dull, steady pain of six months' duration, which was occasionally sharp and stabbing in the lower posterior thoracic and upper lumbar regions radiating through to the epigastrium, and which was worse when the patient was lying down, loss of 30 pounds (13.6 Kg) beginning six months previously, and

constipation and gaseous eructations for two months. About six weeks after admission he became jaundiced. Examination showed moderate emaciation and an enlarged liver. The temperature varied from 97 to 99.4 F. The leukocyte count was 11,000, the erythrocyte count, 5,100,000, and the hemoglobin, 90 per cent. The gastric contents were normal. Roentgen-ray studies were negative. The stools were offensive in odor but contained no occult blood. The clinical diagnosis was carcinoma of the gastro-intestinal tract. Death occurred on Feb. 13, 1922. Autopsy was performed by Dr. L. Smith.

The pathologic diagnoses were carcinoma of the head of the pancreas with metastases to the liver, gallbladder and retroperitoneal lymph glands, icterus, congestion of the liver, spleen and kidneys, chronic inflammatory colitis, central necrosis of the liver, and early arteriosclerosis.

CASE 22—H. F. A., an American, aged 60, was admitted to the hospital on March 3, 1922, with the complaint of blood in the urine. His symptoms were diffuse abdominal pain, constipation, gas and nausea for one month and hematuria for three days. The results of the examination were negative. The temperature was 98 F. The leukocyte count was 9,100, the erythrocyte count, 5,200,000, the urine contained blood. Roentgenograms of the kidney, ureters and bladder were negative. Cystoscopy showed a small growth in the bladder wall. Exploratory laparotomy and excision of a portion of the bladder wall by Dr. Qunby showed carcinoma involving the bladder and sigmoid. Death occurred on March 11, 1922, from postoperative pneumonia. Autopsy was performed by Dr. Hansmann.

The pathologic diagnoses were carcinoma of the tail of the pancreas with metastases to the bladder, intestinal tract and peritoneum, bronchopneumonia (right), empyema (right), intestinal ileus (not due to obstruction), and operative wound of the abdomen and of the bladder.

CASE 23—J. E. T., an American negro, aged 56, was admitted to the hospital on May 22, 1922, with the complaint of epigastric pain. His symptoms were a loss of 18 pounds (8.2 Kg.) beginning eight weeks previously, attacks of dull, aching epigastric pain lasting three or more hours and becoming progressively more severe and progressive jaundice for five weeks. Lying on his right side made the patient nauseated. Examination showed marked jaundice, an enlarged liver and a dilated gallbladder. The temperature was 98.6 F. The leukocyte count was 10,800, the erythrocyte count, 4,000,000, and the hemoglobin, 90 per cent. There was slight glycosuria, the contents of the stomach were normal, there was no blood in the stools, and roentgenograms of the gastro-intestinal tract were negative. The clinical diagnosis was carcinoma of the pancreas. Cholecystoduodenostomy was performed on June 5, by Dr. Cheever. His report was "Gallbladder very tensely distended. The stomach, pylorus and duodenum were normal. A very definite hard, rocklike mass involved the whole head of the pancreas and extended well along the border of the organ. The common duct was normal and palpable down to the mass. There was nothing suggestive of calculus. No metastatic glands were noted anywhere. I am certain this was malignant growth of the pancreas." The jaundice cleared up, and the patient was discharged. No follow-up observations were made.

CASE 24—M. K., a Russian woman, aged 35, was admitted to the hospital on May 21, 1923, with the complaint of pain in the upper part of the abdomen and jaundice. Her symptoms were dull, aching pain in the upper part of the abdomen, the lower part of the back and under the sternum for six months and loss of 40 pounds (18.1 Kg.) in five months. Examination showed moderate emaciation, marked jaundice, an enlarged liver and a dilated gallbladder. The temperature was 99 F. The leukocyte count was 7,600, the erythrocyte count, 5,400,000, and the hemoglobin, 100 per cent. There was no bile or occult blood in the stools which were fatty. There was achlorhydria, and the roentgenograms of the gastro-intestinal tract were negative. The clinical diagnosis was carcinoma of the pancreas. Cholecystogastrostomy was performed, May 31, by Dr. Homans, who made the following observations: "The liver was jaundiced but was without other evidence of disease. The gallbladder was as large as one's fist, tense and

contained 300 cc of white bile. No stones were felt in the cystic or common duct. The head of the pancreas was occupied by a stony hard, irregular mass about 3 inches in diameter. The tail of the pancreas was not thickened. No further exploration was made." Death occurred on June 2, 1923. Autopsy was not performed.

CASE 25—J C M, an Irish woman, aged 76, was admitted to the hospital on Sept 25, 1923, with the complaint of itching. Her symptoms were anorexia and loss of 20 pounds (9 Kg) beginning three months previously and jaundice and weakness for six weeks. The jaundice had diminished for two weeks. Examination showed slight emaciation, moderate jaundice, an enlarged liver and a gallbladder which was palpable part of the time. The temperature was 98 F. The leukocyte count was 6,250, the erythrocyte count, 4,200,000, and hemoglobin, 85 per cent. Bile was occasionally present in the stools. Roentgenograms of the gastro-intestinal tract were negative except for some ptosis and retention in the stomach and duodenum. The clinical diagnosis was carcinoma of the pancreas. Cholecystoduodenostomy was performed under procaine anesthesia on October 10 by Dr Cheever, who made the following observations: "The liver was considerably enlarged and the gallbladder was markedly distended and could not be emptied by pressure. There were no metastases in the liver. In the head of the pancreas a large mass strongly suggestive of neoplasm was felt. Some free fluid was present in the abdomen." The patient was discharged seventeen days after the operation. Death occurred on Sept 20, 1924. Autopsy was not performed.

CASE 26—D F G, an Englishman, aged 57, was admitted to the hospital on Feb 28, 1923, with the complaint of pain in the right upper quadrant and jaundice. His symptoms were dull pain in the midepigastrium associated with nausea, vomiting and anorexia for ten days and jaundice for three days. Examination showed moderate jaundice and a palpable liver and gallbladder. The temperature was 98 F. The leukocyte count was 8,000. There was a slight amount of bile and no occult blood in the stools. The clinical diagnosis was cholelithiasis. Cholecystoduodenostomy was performed on March 10 by Dr Homans, who made the following observations: "The gallbladder was large and tense and thin walled. The common duct was distended. In the region of the head of the pancreas was a rather hard mass which might have been pancreatitis or carcinoma. From this mass running across toward the tail was a definite induration which could not have been cancer. The diagnosis is uncertain. The duodenum was opened and only a small probe could be passed from the common duct into the duodenum. The papilla appeared normal but flattened by the mass in the pancreas. The wall of the duodenum was normal." The patient was discharged relieved, but was readmitted on Sept 26, 1923, complaining of loss of weight and abdominal pain. His symptoms were anorexia, weakness and loss of 14 pounds (6.4 Kg) since his operation. He had been irrational for four weeks. For four days he had had severe sharp pain in the lower part of the back. Examination showed marked emaciation, slight jaundice, a hard irregular mass in the right upper quadrant and edema of both legs. Bile was present in the stools. Death occurred on Dec 4, 1923. Autopsy was performed by Dr Wolbach.

The pathologic diagnoses were carcinoma of the pancreas with invasion of the duodenum by direct extension, glomerulonephritis, bronchiectatic abscesses, edema of the lungs, slight scirrhus of the liver, calcification of old abdominal operative wound and hydropericardium.

CASE 27—W F B, an American, aged 49, was admitted to the hospital on Oct 31, 1923, with the complaint of jaundice and pain in the right costovertebral angle. His symptoms were a loss of 17 pounds (7.7 Kg) beginning six months previously, attacks of dull pain in the right costovertebral angle radiating to the front of the abdomen, anorexia, vomiting and epigastric distress for six months and jaundice for two weeks. Examination showed definite jaundice and a slightly enlarged liver. The temperature was 98 F. The leukocyte count was 6,000, the erythrocyte count, 4,500,000, and the hemoglobin, 95 per cent. There was no bile

or blood in the stools. The urine contained bilirubin, urobilin and bile salts, there was no achlorhydria. Roentgen-ray examination showed no gallstones. The clinical diagnosis was catarrhal jaundice. The patient was discharged for treatment. The jaundice did not recede, and an exploratory laparotomy was performed in another hospital about Jan 1, 1924, by Dr Brewster, who reported "Extensive carcinoma of the head of the pancreas was found." Death occurred about Jan 10, 1924. Autopsy was not performed.

CASE 28—R D W, a Russian woman, aged 44, was admitted to the hospital on March 24, 1923, with the complaint of jaundice and pain in the right upper quadrant. For five years she had had epigastric distress after meals. Her symptoms were heavy fulness in the epigastrium, nausea and vomiting with attacks of severe sharp pain in the right upper quadrant radiating to the right scapular region, loss of 10 pounds (4.5 Kg) during the preceding three months and jaundice which began three months previously and had been fading for one week. Examination showed slight emaciation, moderate jaundice and a palpable liver and gallbladder. The temperature varied from 98 to 99.4 F. The leukocyte count was 12,000, the erythrocyte count, 3,900,000, and the hemoglobin, 75 per cent. There was no bile or blood in the stools. The clinical diagnosis was carcinoma of the pancreas. Exploratory laparotomy was performed on March 28, by Dr Homans, who made the following observations: "A tense gallbladder was presented with a nodule of carcinomatous-looking tissue on the outer surface where it meets the liver. The surface of the gallbladder was smooth, but it presented small nodules on the under surface. There were several cancerous nodules in the liver. In the head of the pancreas was a hard, irregular mass giving the impression of cancer of the pancreas. The stomach was normal." Death occurred on the following day. Autopsy was not performed. Pathologic examination of a piece of tissue from a nodule in the liver showed adenocarcinoma.

CASE 29—M V, an American negress, aged 50, was admitted to the hospital on Jan 28, 1924, with the complaint of jaundice and itching. For fifteen years she had suffered from attacks of colicky epigastric pain associated with nausea and vomiting. These attacks had ceased seven months before entry, and at that time a loss of weight began which had amounted to 35 pounds (15.9 Kg). Jaundice had appeared two months before entry. Examination showed slight emaciation, marked jaundice, an enlarged liver and a dilated gallbladder. The temperature varied from 98 to 99 F. The leukocyte count was 10,000, the erythrocyte count, 4,700,000, and the hemoglobin, 90 per cent. There was no bile or blood in the stools. The clinical diagnosis was carcinoma of the pancreas. Cholecystoduodenostomy was performed on February 5 by Dr Homans, who made the following observations: "The gallbladder was large, smooth, tense and filled with greenish-black material. The liver was firm but not suggestive of hepatic malignancy. A hard mass was felt in the head of the pancreas. No stones were found. The common duct was dilated to the size of a finger. The stomach appeared normal." The patient was relieved and discharged. Death occurred on June 29, 1924. Autopsy was not performed.

CASE 30—S A F, an American woman, aged 69, was admitted to the hospital on Oct 16, 1924, with the complaint of gaseous eructations. Her symptoms were epigastric distress, nausea, and vomiting, anorexia and loss of weight for six weeks. The vomitus consisted of large amounts of food. Examination showed moderate emaciation, a dilated stomach and a hard irregular mass in the epigastrium which did not descend with respirations and which transmitted the aortic pulsations. Auricular fibrillation with a pulse deficit was present. The temperature varied from 98 to 99 F. The leukocyte count was 9,300, the erythrocyte count, 6,400,000, and the hemoglobin, 95 per cent. The gastric contents contained no free hydrochloric acid, the stools contained occult blood. Roentgen-ray studies showed a filling defect in the greater curvature of the stomach, which appeared to be due to an extragastric compression. The clinical diagnosis was carcinoma

of the pancreas Death occurred on Nov 9, 1924 Autopsy was performed by Dr Oughterson and Dr Brown

The pathologic diagnoses were bronchopneumonia (streptococcus), carcinoma of the pancreas with erosion in the small intestine, partial intestinal obstruction, metastatic carcinoma in the liver and pleural adhesions (left apex)

CASE 31—F I V, an American woman, aged 41, was admitted to the hospital on April 24, 1924, with the complaint of stomach trouble Her symptoms were a loss of 17 pounds (7.7 Kg), dull pain in the region of the left costal margin and constipation of three and one-half months' duration The results of examination were negative The temperature was 98 F The leukocyte count was 5,700, and the hemoglobin, 100 per cent Roentgenograms of the gastro-intestinal tract and gallbladder and a pyelogram were negative The patient was discharged without a diagnosis, but was readmitted on July 10, 1924, with the complaint of jaundice, abdominal pain and enlargement of the abdomen Her symptoms were pain and pressure in the epigastrium radiating to the back and to the front of the chest and made worse by food or by lying down, nausea, vomiting, anorexia and loss of 47 pounds (21.3 Kg) in the preceding six months, and jaundice for three days Examination showed moderate emaciation, moderate jaundice, small areas of hemorrhage into the skin and marked ascites The temperature was 99 F The leukocyte count was 7,600, and the erythrocyte count, 5,600,000 There was a trace of bile and occult blood in the stools The clinical diagnosis was carcinoma of the pancreas Exploratory laparotomy was performed on July 12 by Dr Cheever, who made the following observations "About 7 liters of straw colored fluid were removed The liver, stomach, small and large intestine, pelvic viscera, kidneys and spleen were normal to palpation The head of the pancreas was occupied by a hard mass which was continuous with a more nodular mass in the region of the celiac axis There were no implantations in the peritoneal cavity, and no glands were accessible The gallbladder was distended" Death occurred on Aug 15, 1924 Autopsy was performed by Dr Pinkerton and Dr Oughterson

The pathologic diagnoses were carcinoma of the pancreas with metastases to the liver, lungs, peritoneum and mediastinum, biliary stasis, ascites, compression of the portal vein, central necrosis of the liver, cysts of the kidney, healed tuberculosis of the bronchial lymph nodes, and accessory spleen

CASE 32—H S D, an American, aged 60, was admitted to the hospital on Aug 13, 1925, with the complaint of pain and jaundice His symptoms were a loss of 15 pounds (6.8 Kg) during the past three months, a constant dull ache in the epigastrium with attacks of sharp severe pain in the right upper quadrant radiating to the umbilicus, left upper quadrant and, to a slight extent, to the back, accompanied by nausea and weakness for two months, and progressive jaundice for one month Examination showed slight emaciation, moderate jaundice, a palpable liver and a distended gallbladder The temperature was 98 F The leukocyte count was 13,600, and the hemoglobin, 80 per cent The stools were clay colored The clinical diagnosis was carcinoma of the pancreas Cholecystoduodenostomy was performed on August 15, by Dr Cheever, who made the following observations "The gallbladder was very much distended The head of the pancreas presented a hard nodular mass twice the thickness of the normal gland No involved lymph nodes could be found The stomach and pylorus were normal There were several small nodules on the surface of the liver that were typical of carcinoma metastasis There were no gallstones in the gallbladder or gallducts" The patient was discharged relieved

CASE 33—E L S, an American woman, aged 70, was admitted to the hospital on Aug 27, 1925, with the complaint of pain in the stomach and back Her symptoms were attacks of dull, pressing pain in the epigastrium radiating through to the back and unassociated with food, loss of 30 pounds of weight (13.6 Kg) and anorexia for eight months Progressive jaundice and weakness had been present for three weeks Constipation had increased and gaseous eructations nausea and vomiting had accompanied the attacks of pain Examination showed

marked emaciation and weakness, moderate jaundice, a palpable liver, a distended gallbladder and fluid in the abdomen. The temperature was 97 F, the pulse rate, 102. The leukocyte count was 25,000, the erythrocyte count 4,600,000, and the hemoglobin, 60 per cent. Roentgenograms of the gastro-intestinal tract, kidney, gallbladder and chest were negative. The Wassermann reaction was positive. The clinical diagnosis was carcinoma of the pancreas. Death occurred on Aug 31, 1925. Autopsy was performed by Drs Connors and Blosser.

The pathologic diagnoses were adenocarcinoma of the head of the pancreas with extension into the stomach and duodenum, metastases to the peritoneum, liver and retroperitoneal glands, and obstructive jaundice.

INCIDENCE OF THE DISEASE AS REGARDS SEX AND AGE

Sex—Of the thirty-three cases, eighteen occurred in men. The predominance of men over women in the incidence of pancreatic cancer is not so striking here as in most other reported series. Table 1 indicates that almost twice as many men are affected.

TABLE 1—*Carcinoma of the Pancreas in Relation to Sex as Shown in the Literature*

Author	Men	Women
Miralhe	69	35
Dr Costa	24	13
Boldt	35	21
Speed	36	16
Futcher	22	9
Ancelet	102	59
Total	288	153

TABLE 2—*Cases of Carcinoma of the Pancreas in Relation to Age*

Age in Years	Oser's Series	Brigham Hospital Series
1 to 10	1	0
11 to 20	1	0
21 to 30	3	0
31 to 40	14	2
41 to 50	19	9
51 to 60	20	12
61 to 70	10	6
71 to 80	4	4

Bashford found 526 cases among 33,788 autopsies on men and 474 cases among 50,660 autopsies on women.

Age—The ages in the thirty-three cases ranged from 33 to 76 years with an average of 56.5 years. The average of the men was 57.5 and the average of the women was 55 years. The distribution of the cases in the different decades is given in table 2.

The age incidence is comparable to that of cancer in general, the disease occurring in rare instances in children. Herringham reported a case in a girl aged 2 years.

ETIOLOGY

The cause of carcinoma of the pancreas lies in the obscurity of the etiology of cancer in general. In accordance with the theory of chronic irritation, chronic pancreatitis, syphilis and alcohol have been suggested

as possible factors, but with little evidence Ewing¹⁸ suggests that tumors might sometimes arise from the accessory glandular tissue Horgan¹⁹ endeavored to establish a relationship between carcinoma arising in the islands of Langerhans and the chronic pancreatitis which is often found in cases of peptic ulcer In 262 pancreases showing chronic fibrotic changes he found hypertrophic islands in forty-eight Histologic study of the enlarged islands revealed hyperplastic epithelium with little or no differentiation and in some cases evidence of migration He points out that the three stages of neoplasia described by McCarty are present The past histories of the Bingham Hospital cases were on the whole negative, revealing no clue to an etiologic factor One patient had had gallstones and three others had had digestive troubles, which might possibly have been due to peptic ulcer

SYMPTOMS

The most common symptoms in the thirty-three cases studied were in the order of their frequency cachexia—including loss of weight anorexia, weakness and anemia—jaundice, pain, nausea with or without vomiting, indigestion and constipation In his series, Speed found cachexia in 90 per cent, jaundice in 80 per cent and pain in 61 per cent of the cases Although cachectic symptoms are the most frequent, it is usually jaundice or pain that causes the patient to seek medical advice In seventeen of the thirty-three cases the chief complaint was jaundice, and in nine it was pain Four patients came to the hospital because of indigestion, while one complained of swollen glands, one of hematuria and one of pallor

Cachexia—Cachectic symptoms occurred in twenty-nine of thirty-three cases and were as a rule extreme and out of all proportion to the size of the growth This is probably due to the obstructive jaundice which commonly occurs, a complication which greatly depresses the appetite as well as interferes with the absorption of food

Loss of Weight Loss of weight is the most outstanding of the cachectic symptoms and was present in twenty-eight of thirty-three cases In at least twenty-two cases it was the first symptom noticed by the patient The amount of weight lost is usually large In the series of thirty-three cases the greatest loss at the time the patient was admitted to the hospital was 50 pounds (22.7 Kg), the average loss, 28 pounds (12.7 Kg) In each of seven cases there was a loss of 40 pounds (18.1 Kg) or more The rate at which the loss in weight takes place is usually strikingly rapid In one instance there was a loss of 41

18 Ewing, James Neoplastic Diseases, Philadelphia and London, 1922, p 702

19 Horgan, E J The Histogenesis of Carcinoma in the Islets of the Pancreas, J Lab & Clin Med 5 429 (April) 1920

pounds (186 Kg) in six weeks. The average rate of loss in weight for the group was estimated at 5 pounds (23 Kg) a month. Fitcher found rapid and extreme emaciation in twenty-nine of thirty-one cases.

Anorexia Loss of appetite is a common symptom, occurring in twenty cases. It is particularly severe when there is jaundice.

Weakness Loss of strength practically always accompanies a marked loss of weight and was complained of twenty-one times.

Jaundice—Jaundice, the second most common symptom, is obstructive in type and characterized by its extreme degree and progressiveness. Unlike the intermittent jaundice which frequently accompanies obstruction of the common duct by gallstones, the jaundice of pancreatic malignancy once begun progresses relentlessly until in some cases the so-called "black" jaundice is produced which may be so pronounced that the patient may be mistaken for a negro. When the jaundice has persisted for many weeks, the pigments deposited in the exposed tissue of the face and hands become changed by the action of light to a dark greenish hue which may be almost black.

Itching of the skin was present in one third of the cases.

In 60 per cent of the normal persons the common bile duct is completely surrounded at its lower end by the head of the pancreas. In the remaining 40 per cent the duct lies in a groove between the gland and the duodenum. Since a large proportion of pancreatic tumors occur in the head of the pancreas, the common duct is apt to be occluded early by outside compression, by infiltration of the duct wall or by growth into the lumen of the duct. Jaundice may also be produced by obstruction of the hepatic duct by a metastatic nodule in the liver, even though the primary growth is in the tail of the pancreas (case 15). The occlusion of the duct is apt to become complete in a short time, so that bile is totally excluded from the intestine. In sixteen of nineteen cases of jaundice bile was totally absent from the stools. Parmentier and Chabrial call attention to the fact that the jaundice is not a dissociated jaundice, but that the bile acids and bile salts are retained as well as the bile pigments. They also state that the jaundice may decrease in the last weeks of life owing to a damaged liver and resultant acholia. In three of the cases in the Brigham Hospital there was a possibility of some reduction in the degree of jaundice, but in no case was the jaundice definitely intermittent.

Jaundice occurred in eighty-three of the 113 cases collected by Mallie and in twenty-three of the thirty-one cases reported by Fitcher. They both state that it is often the first symptom. In the thirty-three cases from the Brigham Hospital, jaundice occurred twenty-five times. In three instances it was the first symptom to appear, and in eleven cases it was the second.

Pain—Pain was a prominent symptom in twenty-one cases. It was the first manifestation of the disease in four instances and the second in three. Speed reported that pain was severe in 61 per cent of fifty-two cases. It was an important symptom in fifty-six of 113 cases collected by Mirallie and in twenty-five of the thirty-one cases in the Johns Hopkins Hospital.

In general there are three types of pain associated with cancer of the pancreas. One type is a steady, dull, severe, midepigastriac pain radiating to the lower part of the back. Another type occurs in paroxysms of severe pain beginning near the umbilicus and radiating to the back and front of the chest, and a third type is a colicky pain in the right hypochondrium sometimes radiating to the right subscapular region, fairly similar to gallstone colic. Mirallie describes the pain of pancreatic carcinoma as occurring in paroxysms of severe, sharp pain, boring or tearing in character, present in the entire epigastrium and radiating to the back at the level of the twelfth dorsal and first lumbar vertebrae. It may also radiate to the front of the chest, abdomen and lower limbs. The paroxysms are sometimes brought on by food and sometimes by lying down. Several cases have been reported in which the patient had the pain only when he lay on his back and was relieved when the body was flexed. Vomiting may accompany the pain, which may last for an hour or for any irregular period of time. There are several different theories of the mechanism of the pain production. Lucron²⁰ believed that the paroxysms were produced by pressure on the celiac plexus by the tumor mass. The pain has also been attributed to bile stasis and to pancreatic obstruction. Speed noted that the pain was relieved in many of the patients on whom cholecystostomies or cholecystenterostomies were performed. In thirteen of the thirty-three cases the first type of pain was present. In all thirteen the head of the pancreas was occupied by a tumor, and also in ten of the thirteen instances the pain had been present for several weeks before the onset of jaundice. In the remaining three, jaundice did not appear. There was radiation of the pain to the lower part of the back in eleven of the thirteen cases. In six there was a definite relationship between the pain and the position of the body, the pain being worse when the patient was lying down and relieved by sitting up or by flexing the body.

The paroxysmal type of pain occurred in five cases. The head of the gland was occupied by a tumor in three cases, the body in one and the entire pancreas in one, and the tumor masses were larger than the average tumor found. In all five the onset of pain was earlier than the onset of jaundice. The radiation of the pain was to the front of the chest in two cases and to the back in two cases.

20 Lucron, quoted by Mirallie (footnote 5)

In three cases colic occurred in the right upper quadrant. The head of the pancreas was occupied by tumor in all three, and jaundice was present in all, having preceded the pain in two. The gallbladder was distended in all three, but there were no gallstones.

Apparently one patient may suffer from two types of pain. He may have the constant, dull, epigastric pain, and he may occasionally have attacks of the paroxysmal variety.

Nausea and Vomiting—Nausea with or without vomiting was an important symptom in twenty of the thirty-three cases. It is a common accompaniment of attacks of pain or distress, and sometimes the patient suffers from almost constant nausea. Stimulation of the branches of the vagus has been suggested as one cause of nausea and vomiting. Vomiting may be secondary to intestinal or pyloric obstruction. In case 2 the patient vomited large quantities of stomach contents, and at autopsy the stomach was found to be enormously dilated. Undoubtedly the exclusion of bile and pancreatic secretion from the intestine, together with the reduction of gastric acidity, is responsible for considerable nausea and vomiting.

Gastro-Intestinal Distress—Epigastric distress not amounting to real pain is a common complaint. Seventeen of the thirty-three patients gave a history of this symptom. One of the most common descriptions is that food seems to stick in the stomach and lies there as a heavy mass in the midepigastrium. Oppression, heartburn and constriction about the chest were other terms by which the patients described this symptom. Gaseous eructations sometimes accompany the distress.

Intestinal Disturbances—Constipation is the rule, being definitely brought on or increased in sixteen cases. In no case was there a complaint of diarrhea. Constipation is a well known sequel of a lack of bile in the intestine, but even in the cases without jaundice constipation was almost a constant observation.

Edema—Edema of the legs occurred in ten cases, in three of which a partial obstruction of the vena cava was found. In two, cardiac weakness was apparently the cause, and in one, in which the edema was confined to one leg, there was an intercurrent thrombosis of the iliac vein. In the remaining four, no anatomic explanation was found, and the edema can probably be ascribed to inanition.

Ascites—Free fluid in the abdomen was present in three cases. In one there was cardiac decompensation, in another the fluid was due to a generalized carcinomatosis of the peritoneum, and in the third there was obstruction of the portal vein. Speed reported ascites in 20 per cent of his series. Cases of chylous ascites due to obstruction of the thoracic duct by cancer of the pancreas are not rare in the literature.

Hematuria—Bloody urine was the chief complaint of one of the patients. In this case the carcinoma was situated in the tail of the pancreas but had metastasized to the wall of the urinary bladder. Another patient showing hematuria was found to have generalized carcinomatosis involving the left kidney. Cases have been reported of involvement of the left kidney by direct extension of the tumor growth from the pancreas.

Other Symptoms—Miallie states that among the rarer symptoms are multiple hemorrhages, purpura, melena and phlegmasia alba dolens. Speed reports hemorrhage as a frequent symptom probably due to ruptured varices of the gastro-intestinal tract.

PHYSICAL SIGNS

Emaciation is the most common physical observation. This was observed in twenty-four cases, in two of which the degree of emaciation is recorded as extreme, in seven, as slight.

Jaundice—Jaundice was observed at the first examination in twenty-three cases, and in two others it developed after admission to the hospital. The jaundice was of extreme degree in thirteen cases.

Pigmentation of the Skin—According to Parmentier and Chabral, there may be a brownish pigmentation of the skin, particularly over the epigastrium, similar to that in Addison's disease. This is due either to an invasive destruction of the suprarenal or to an irritation of the splanchnic sympathetic nerves.

Liver—Because of the usually associated emaciation, the abdominal organs are, as a rule, easily palpated. The liver was felt in twenty-six cases, in fifteen of which it was definitely enlarged. The enlargement was due in most cases to bile stasis, Bard and Pic having pointed out that the liver metastases are usually small instead of bulky. A metastatic nodule can rarely be felt through the abdominal wall, and the liver edge is usually not tender. Miallie reported the liver enlarged in seventeen of 113 cases, and stated that the enlargement tended to disappear in the course of the disease owing to destruction of the liver tissue.

Gallbladder—A dilated gallbladder was felt in fifteen of twenty-three cases of jaundice, it was dilated in two of the remaining eight cases, but was not felt at examination. In one instance the gallbladder had been removed previously for gallstones, and in two others the gallbladder was thickened and showed evidence of a chronic cholecystitis. In one case the jaundice was due, not to obstruction of the common duct, but to compression of the hepatic duct by a metastatic nodule within the liver substance. In another case the operative note does not describe the gallbladder, and in the remaining case the operator described the gallbladder as distended but not dilated.

Bard and Pic noted the frequency of a palpable gallbladder in jaundice associated with carcinoma of the pancreas, and later Courvoisier pointed out its value in the differential diagnosis between common duct obstruction due to malignant disease and that due to gallstones (Courvoisier's law)

Futcher reported a dilated gallbladder in twenty-one of twenty-three cases of jaundice, and in one the gallbladder was ruptured

Characteristically the dilated gallbladder is felt as a hard, rounded, smooth mass about the size of an egg, situated in the right upper quadrant distinct from and below the liver edge and descending with inspiration

Tumor Mass—A tumor mass, which was not the gallbladder, was felt in nine of the thirty-three cases. Characteristically the mass was hard, irregular and not large. Usually it lies in the midepigastrium but may be felt in either hypochondria. The mass sometimes appears to move slightly with respiration. When it lies over the aorta, pulsations are transmitted to the abdominal wall, and if the aorta is compressed, a systolic bruit may be heard over the tumor. Tenderness is not a marked characteristic

Da Costa found a mass in thirteen of thirty-seven cases, Futcher in twelve of thirty-one and others in about 30 per cent of the cases. In general, it is an inconstant observation

Other Signs—Enlarged peripheral lymph glands was the only observation in one case. An inconstant sign is dilated abdominal veins when the vena cava is obstructed. Intestinal obstruction is sometimes indicated by visible peristalsis and dilatation of the stomach. Edema and ascites have already been discussed, but effusion into the pleural cavities may result from metastatic involvement of the pleura

Fever—In nineteen cases there was a low grade fever present, but in only three did the temperature range above 100 F

Pulse—Bradycardia is not a common accompaniment of the jaundice. In only three was the pulse rate below 70 per minute

Urine—Bile was present in the urine of all the jaundiced cases, usually in large amounts. Some albumin usually accompanies the bile, due to renal irritation

Glycosuria—Although glycosuria has been associated with carcinoma of the pancreas from the first, genuine diabetes appears to be a rare coincidence. In only two of the Brigham Hospital cases was sugar present in the urine, and the amount was appreciable in only one. In this case there was no other symptom of diabetes. The incidence of glycosuria as found by other authors is shown in table 3

Although cases of apparently genuine diabetes have been reported, most of the cases of glycosuria have been of the mild intermittent type. Several authors have noted the apparent total lack of relationship between the amount of pancreas destroyed and the glycosuria. Bard and Pic²¹ concluded that the cases of true diabetes were merely coincidences, and that a mild intermittent glycosuria sometimes resulted when a large part of the pancreas was destroyed.

Since the incidence of diabetes mellitus is greatest in the fifth and sixth decade of life, it is not surprising that there are some cases of diabetes in a group of patients representing the age group in which cancer of the pancreas is found. In the intermittent mild type of glycosuria there are other factors besides the pancreas to be considered. Damage to the liver occurs both by metastatic growth and by bile stasis, which undoubtedly affects the carbohydrate metabolism, and it is generally recognized that many patients with cancer have a lower glucose tolerance.

TABLE 3—*Incidence of Glycosuria in Cases of Carcinoma of the Pancreas*

Author	Number of Cases of Glycosuria	Total Number of Cases
Mirallie	13	50
Guillon	20	71
Pearce	3	30
Speed	3	52
Futcher	3	31
Herringham	1	17

In Joslin's²² series of 5,121 cases of diabetes, the diagnosis of cancer of the pancreas was made in thirteen cases. In only four of these was the diagnosis verified. It appears from these figures that carcinoma of the pancreas is no more frequent among diabetic patients than among any other group of the same age.

Blood—A leukocytosis of over 10,000 was present in fifteen of fifty-three cases. The differential count usually shows a moderate increase in polymorphonuclears.

An anemia of less than 4,000,000 erythrocytes was found in nine of twenty-one cases. In the twelve cases in which the erythrocytes count was not made, the hemoglobin was normal.

In jaundiced patients the blood serum is highly colored and gives a positive direct van den Bergh reaction.

Gastric Contents—Free hydrochloric acid was present after an Ewald meal in eleven of fifteen cases.

²¹ Bard, L., and Pic, Andrien. De la glycosurie dans le cancer primitif du pancreas, *Rev de méd* 17 929, 1897.

²² Personal communication from Dr Elliott P. Joslin, Boston 1926.

Stools—In the twenty-three cases of jaundice, bile was absent from the stools in fifteen. In two cases there was no record of an examination of the stools, while in the remaining six cases bile was present in at least small amounts.

Occult blood was present in the stools of ten of twenty-seven patients.

The amount of fat in the stools was not determined routinely, but in seven instances the stools were recorded as appearing to contain excessive fat. There has been considerable difference of opinion concerning steatorrhea. It is supposed to be the result of obstruction of the pancreatic duct, but the pancreatic juice is not the only digestive secretion concerned in fat absorption. The absence of bile retards the absorption of fat, and fatty stools are common in jaundice. Since the lipase of the pancreatic juice hydrolyzes the fat, theoretically there should be a relative increase in the amount of neutral fat and a decrease in the proportion of fatty acids and soaps. However, there is also a fat splitting enzyme in the intestinal juices which makes the results variable. Pratt, Lamson and Marks²³ obtained variable results when they excluded the pancreatic secretion from the intestine in dogs. The rate of peristalsis is another factor.

Northrup and Hertel²⁴ studied the fat absorption in a single case of carcinoma of the head of the pancreas. They found that 47 per cent of the food fat was lost in the feces, but that there was no appreciable increase in the proportion of neutral fat.

If over 30 per cent of the dry weight of the feces is found to be fat, it is an indication of malabsorption of fat. According to Parmentier and Chabral, microscopic examination of the stools in pancreatic obstruction should show muscle fibers and vegetable cells which appear to be soaked in oil. Undigested nuclei in the muscle fibers are supposed to be particularly significant.

Roentgen-Ray Examination—Roentgen-ray examination of the gastro-intestinal tract is of little positive value in diagnosis. In thirteen cases examined, the roentgenologist was unable to make the correct diagnosis in a single case. In Speed's series the roentgen-ray diagnosis was correct in two of twenty-three cases. The chief value of the roentgen-ray examination is in ruling out cancer of the gastro-intestinal tract, which can be done with about 90 per cent of accuracy. When the pancreatic tumor is small, the roentgen ray cannot be expected to show a lesion, but when the head of the pancreas is occupied by a large tumor, there is a characteristic displacement of the first and second

23 Pratt, Lamson, and Marks, quoted by Hewlett, A. W. *Pathological Physiology of Internal Diseases*, New York and London, 1923, p. 184.

24 Northrup, W. P., and Herter, C. A. *Carcinoma of the Pancreas*, *Am J Med Sc* **117** 131 (Feb) 1899.

portions of the duodenum to the right, and there may be a displacement of the third portion downward, so that the duodenum is seen to make an abnormally broad sweep around the region of the head of the pancreas. When a tumor of considerable size is situated in the tail of the pancreas, a pressure deformity of the greater curvature of the stomach may be seen.

Duration—The duration of life after the onset of symptoms is given by Bard and Pic as from six to seven months, by Miallie as from four to five months, and by Parmentier and Chabral as from four to seven months. The duration depends on the rapidity of growth and on the degree of compression of vital structures. On the whole, the disease is rapidly fatal, due to the strategic anatomic position of the growth.

In the Brigham Hospital cases, the time elapsing between the onset of the first symptom and the admission of the patient to the hospital varied from ten days to one year, with an average of four and three-tenths months. In only eight instances had the patient had symptoms for more than six months. The duration of life after admission to the hospital ranged from four days to one year, with an average for thirty-one cases of two and three-fourths months. In only nine cases did life extend over four months. The total duration of life from the onset of the first symptom varied in thirty-one cases from seven weeks to seventeen and two-tenths months with an average of seven and three-tenths months. Five patients lived less than three months after the appearance of the first symptom, and ten lived for more than eight months.

PATHOLOGY

On the whole, death occurs before the tumor has grown to a large size, but in ten of the thirty-three cases the tumor mass was large enough to measure at least 6 cm. in its greatest diameter. The largest tumor was found in case 31. It measured 16 by 9 by 7 cm. and weighed 640 Gm. The large tumors have their origin in the body or tail of the pancreas. Tumors as large as a child's head have been reported.

The gross appearance of the tumor was described in almost every case as a hard, dense, lobulated, coarsely nodular mass. On section it is grayish or yellowish white and usually shows evidence of infiltration. Often there is central necrosis, which may or may not cause fever and leukocytosis. According to McFarland,¹⁷ some carcinomas of the pancreas are soft and massive, and in rare cases they are gelatinous.

The situation of the cancer is usually in the head of the pancreas, as it occurred in twenty-four of thirty-three cases. In three cases the body of the gland appeared to be the original site, and in two cases the tumor was confined to the tail. Four pancreases showed total involvement by the tumor growth. In table 4 is shown the location of the growth as found in other series.

Since the work of Baird and Pic in 1888, two distinct histologic types of pancreatic carcinoma have been recognized. One type is represented by cylindric epithelial cells, which are thought to have their origin in the proliferation of the duct epithelium. The tumors of this type are most apt to be scirrhous in character, and sections show disseminated lobules in large amounts of fibrous tissue. The lobules are composed of many ramifications with large lumina and a wall of a single layer of columnar cells showing abnormal mitotic figures. In some sections the structure may be less tubular and show detached groups of cells invading the surrounding tissue.

The second type of carcinoma arises from the parenchymal or acinar cells of the pancreas. The cells in this type are large, polyhedral and contain large round or oval nuclei. They are apt to be found scattered separately in a fine delicate stroma, in small groups or cords, or in acinar-like arrangements. There is much less fibrous tissue present, and sometimes the sections appear much like chronic pancreatitis. The same characteristics and arrangements are found in the metastases.

TABLE 4—*Location of the Growth in Cases of Carcinoma of the Pancreas*

Author	General	Head	Body	Tail
Lancereux	—	11	2	2
Mirallie	19	39	3	4
Oser	1	20	2	3
Boldt	18	25	5	5

The islands of Langerhans apparently do not give rise to carcinoma, although Fabozzi²⁵ concluded that all types of pancreatic carcinoma arise from the islet tissue. Hypertrophied islands occur which may be considered adenomatous, these have been described by Le Comte²⁶. He reported a case in which a single island was found which measured 10 cm. in its greatest diameter.

In eighteen cases of the Brigham Hospital series in which the histology could be studied by autopsy or biopsy, the columnar or duct type of cell was found in cases 4, 7, 14, 21, 22, 26, 30 and 33. The acinar or parenchymal cell was found in cases 2, 3, 11, 15, 16, 17, 19 and 20. In case 31 there appeared to be a mixed histology, both types of growth being present. Case 28 showed a cell which was not typical of a pancreatic cell, and the tumor apparently originated in the gall-bladder.

It was impossible to determine any relationship between the type of growth and the metastatic or infiltrative activity, size of the tumor, location of the mass, necrosis or duration of life.

²⁵ Fabozzi. Beitr. z. Path. Anat. u. z. allg. Pathol. **34** 199, 1903.

²⁶ Le Comte, R. M. Adenoma of the Islands of Langerhans, J. M. Research **24** 251 (Dec.) 1913.

Of thirty-three cases of carcinoma, the growth was primary in the pancreas in thirty. In case 11 a carcinoma of the duodenum had ulcerated into the pancreas so that pancreatic tissue was exposed to the lumen of the duodenum. The bile duct was the primary focus in case 12 and the gallbladder in case 28. Some authors assert that secondary carcinoma in the pancreas is more common than primary carcinoma, and that the stomach is the most important primary region. Secondary growths usually reach the pancreas by direct extension.

A large majority of pancreatic cancers show early metastases chiefly to the lymph nodes along the anterior border of the pancreas, bile ducts and the lesser curvature of the stomach and to the liver. Seven cases showed generalized carcinomatosis. Case 16 showed metastases to the brain. In no case were bony metastases discovered. The metastases are disseminated chiefly through the lymphatics, but the blood stream is often invaded. A spread of tumor growth downward throughout the peritoneal cavity is not uncommon.

Direct extension of the tumor into the surrounding tissue was found in nine cases. The stomach, small intestine, common bile duct, left kidney, left suprarenal and large veins are the organs most commonly invaded. Cases have been reported that have been examples of compression of the gastro-intestinal tract, biliary tracts, portal vein, vena cava, aorta, splenic and mesenteric vessels, thoracic duct, left ureter and renal vessels.

Erosion into the gastro-intestinal tract may give rise to serious hemorrhage. Ulceration about the papilla of Vater may result in the release of bile obstruction. In several cases it was found that although there had been complete obstruction of the flow of bile a probe could be passed into the common duct and bile could be forced into the duodenum by pressure on the gallbladder, thus showing that the common duct is sometimes collapsed without being infiltrated.

The portion of the pancreas that is not invaded by tumor usually shows the fibrous changes of chronic pancreatitis. The islands of Langerhans tend to persist and are found even within the tumor tissue. In the border region between tumor and pancreatic tissue the islands are often hypertrophied and much more numerous than normal, analogous to the conditions which are produced in animals by ligation of the pancreatic duct. The acinar tissue atrophies, allowing the islands to come closer together.

The liver suffers from biliary stasis, central necrosis and cirrhosis. The liver metastases are usually small, because death occurs before they have time to attain a large size.

DIAGNOSIS

When jaundice is present, the most important condition in the differential diagnosis is obstruction of the common duct by gallstones. The jaundice in malignancy is practically always progressive and unemitting in character, while in cholelithiasis the jaundice is usually intermittent. In cholelithiasis the history is longer and characterized by a long period of attacks of indigestion, colic and fever. Cachexia is an important differential sign, because it is present in practically all cases of cancer that have progressed to the point of producing jaundice, although it must be remembered that large losses of weight sometimes occur in cases of long-standing jaundice due to gallstones. When a dilated gallbladder can be palpated in the presence of jaundice of the progressive type, the diagnosis of carcinoma is probably correct, although Courvoisier's law is not infallible. The gallbladder is occasionally dilated in jaundice due to a common duct stone, as was found eight times in twenty-four operations for this condition at the Brigham Hospital. In only four of the eight cases was it possible to palpate the dilated gallbladder, because of the obesity of the patient and the thickness of the abdominal wall. Ecklin's²⁷ statistics on 172 cases of obstruction of the common duct due to gallstones showed the gallbladder contracted in 110, normal in thirty-four and dilated in twenty-eight. In 139 cases of obstruction not due to gallstones, the gallbladder was contracted in nine, normal in nine and dilated in 121. When a tumor mass can be palpated in the region of the head of the pancreas, or if ascites develops later, the diagnosis of carcinoma is more certain.

Infectious jaundice and catarrhal jaundice are differentiated by the onset and course. Fever is not prominent in carcinoma unless the cachexia is marked.

Chronic pancreatitis may cause a clinical picture similar to that of carcinoma, and it is difficult to distinguish between them even when the abdomen is open, unless the operator can find metastases in the liver. In chronic pancreatitis with obstruction of the common duct there is usually a long previous period of illness.

It is practically impossible to distinguish obstruction of the common duct by carcinoma arising in the liver, gallbladder, bile ducts or ampulla of Vater.

When there is no jaundice, the diagnosis is even more difficult, unless a tumor can be felt or unless an external pressure deformity of the stomach is shown by the roentgen ray. A tumor mass in the region of the body or tail of the pancreas is to be differentiated from carcinoma of the stomach or other adjacent organ, pancreatic cyst, enlargement of the retroperitoneal glands and abdominal aneurysm. Roentgen-ray

27 Ecklin, Inaugural Dissertation, Basel, 1896

examination by means of the opaque meal or pyelogram is valuable in ruling out cancer of the gastro-intestinal tract and of the left kidney. A pancreatic cyst is excluded by its physical characteristics and by the usual absence of cachexia. General glandular enlargement is not usually found in carcinoma of the pancreas. A tumor mass in the pancreas will transmit the aortic pulsations, but the pulsations are not expansile.

The preoperative diagnosis was correct in nine of nineteen cases of the Brigham Hospital series.

SPECIAL TESTS

It would seem that the presence or absence of glycosuria is of less significance than is generally supposed. A quantitative estimation of the fat content of the stools is of value but is not conclusive.

Duodenal drainage and an analysis of the contents for bile and pancreatic ferments has been particularly advocated by Crohn.²⁸ He finds that the absence of the least trace of bile is rare, except in malignant obstruction. Trypsin diastase and pancreatic lipase are detected in the duodenal contents by the digestive action of the fluid on egg white, soluble starch and butter fat when incubated and compared with the action of a control in which the ferments have been destroyed by heat. Practically all of the special tests used in pancreatic disease have been reviewed by Decker,²⁹ and his conclusions were that none of the tests are reliable. Unfortunately, the duodenal contents were not examined in a sufficient number of the cases reported here to warrant any conclusions as to its diagnostic value. In accordance with the theory that in pancreatic obstruction there is an absorption of the external secretion of the pancreas by the blood analogous to the cholemia which is found in the obstruction of the bile tract, Wohlgemuth³⁰ devised a test for amylase in the blood and urine. Since then his technique has been modified and his observations of amylaemia have been confirmed by Geyelin,³¹ Corbet³¹ and Noguchi.³²

TREATMENT

The treatment of carcinoma of the pancreas is unsatisfactory. At best it is only palliative and symptomatic. Exploratory laparotomy is nearly always indicated on the grounds of a possibly mistaken diagnosis, and the patient may be cured by the removal of an impacted gallstone.

28 Crohn, Burrill B. New Growths Involving the Terminal Bile Ducts, Their Early Diagnosis by Means of Duodenal Contents Analysis, *Am J Med Sc* **148** 839 (Dec) 1914.

29 Decker, H. Ryerson. The Recognition of Pancreatic Insufficiency with Special Reference to the Loewi Test, *Boston M & S J* **176** 867 (June) 1917.

30 Wohlgemuth, quoted by Noguchi (footnote 32).

31 Geyelin and Corbet, quoted by Decker (footnote 29).

32 Noguchi, Y. Ueber die Fermentdiagnose bei Pankreasverletzung, *Arch f klin Chir* **98** 545 (May 21) 1912.

from the common duct. If cancer is found, it is usually comparatively easy to anastomose the dilated gallbladder to the duodenum, a procedure that opens a new route for the passage of bile into the intestine. Although life may not be materially prolonged, the patient is made much more comfortable, particularly if there has been much pruritus or gastric distress associated with the jaundice. The usefulness of the gallbladder in such situations make it unwise to remove the gallbladder during operations for disease of the biliary tract unless the possibility of pancreatic carcinoma seems remote.

Excision of the tumor is rarely feasible because of the early metastasis. Operation on the pancreas is extremely difficult because of the inaccessibility of the organ, the danger of hemorrhage and the loss of pancreatic juice in the peritoneum. Sutures are quickly digested by the pancreatic ferments, which are toxic when mixed with blood.

Finney³³ in 1910, reported a case in which he had removed a large tumor from the body of the pancreas. The body of the pancreas was removed with it, and the head and the tail of the organ were sutured together, packed off and drained. The patient was in perfect health sixteen months later. Finney found sixteen other cases of resection of the pancreas for primary tumor in the literature. Nine of the seventeen patients recovered, in three of these the pancreas had been completely divided. Kausch³⁴ advocates surgical treatment in two stages. The first stage is a cholecystenterostomy, and after recovery from the jaundice radical excision of the tumor, including the head of the pancreas. The pancreas is then implanted into the lower end of the duodenum, and a gastro-enterostomy is performed if necessary. Radwitz³⁵ reports that the immediate mortality in radical operations for cancer of the pancreas is 50 per cent, and that no patient survives more than five months.

Successful treatment with roentgen rays has not been reported.

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33 Finney, John M. T. Resection of the Pancreas, *Ann Surg* **51** 818 (June) 1910

34 Kausch, quoted by Crohn (footnote 28)

35 Von Redwitz, E. Surgery of the Pancreas, *Munchen med Wchnschr* **71** 1561 (Nov 7) 1924, *abstr J A M A* **83** 2053 (Dec 20) 1924

THE PATHOLOGY OF METABOLISM IN OBESITY

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The anomaly of human bodily structure most often encountered is excessive storage of fat and, as a consequence, abnormal increase in weight. Only a few investigations have been made to ascertain the cause.

Obesity is generally divided into two groups: endogenous and exogenous, but a sharp distinction between the two has not been drawn. Some investigators consider as endogenous obesity only that type in which symptoms other than corpulence indicate an endocrine disease, while others are of the opinion that ultimately almost all cases of obesity are exogenous. However, there is much confusion on this point. It is certain that a regulation of the body weight takes place. When we consider what minimal amounts of fat must be stored per day in order to produce a considerable increase in weight and compare them with the daily intake of food, it is easily seen that this regulation must be delicate, so that it seems improbable that the appetite should be the only regulating factor. This is evident from the fact that many persons are induced by habit and external conditions to take amounts of food which cannot possibly depend exclusively on their appetite. The problem, therefore, cannot be put as a simple addition and subtraction of the intake and expenditure of the organism. If the regulation by the appetite is disregarded, so that the person constantly eats more than he needs—and certainly large excesses play a rôle in many cases—one is forced to adopt the view that a regulation takes place in the combustion of the foodstuffs, otherwise the weight of such a person would increase rapidly. Experience shows, however, that in spite of the consumption of large amounts of food, the weight of many persons does not vary. Therefore there must be a regulation independent of the appetite. Obesity cannot be due exclusively to overnutrition, but to a disturbance of the regulation of the combusive processes in the organism. Our idea was to investigate to what extent obesity could be considered as a qualitative anomaly of metabolism, more or less analogous to diabetes mellitus. Most previous authors have considered the problem as a purely quantitative question of the intake and expenditure of calories.

As obesity frequently accompanies or is a precursor of both light and severe cases of diabetes, we started from the working hypothesis that obesity in many cases might be due to an abnormally increased

transformation of carbohydrate into fat This article contains an experimental study of the hypothesis

When we planned our work, investigations by one of us (H C H)¹ were at hand From these it seemed evident that by using the method which most naturally might be employed to solve the problem, that is, the determination of the respiratory quotient after the intake of carbohydrate, we would be confronted with serious difficulties It was necessary to make several experiments on the same person within a few hours, and it was feared that the whole experimental method, even if the experiments might solve the problems, would become so difficult that the clinical employment of the method would be impossible

Therefore, we planned the following experiments We knew from Krogh and Lindhard's work² that a diet consisting mainly of carbohydrates causes the respiratory quotient in the postabsorptive state to rise to a high level If some persons transform a great amount of carbohydrates into fat shortly after their intake, and consequently have a higher quotient than normally shortly after the meal, they must have a lower quotient than normal persons on the following morning, in the post-absorptive state Hence our aim was to determine whether obese persons living on a diet consisting mainly of carbohydrates have a lower quotient in the postabsorptive state than normal persons on the same diet

Before describing our experiments, we must refer to the results of some recent work concerning the pathology of metabolism in obesity

Liebesny and Plaut have investigated the specific dynamic action of protein in obese persons and have arrived at interesting conclusions However, they do not seem to be directly related to the problems with which we have been dealing Investigations by Strouse and his co-workers,³ concerning which we did not have any knowledge until after our experiments were finished, are, however, intimately connected with our problem Our investigations, in fact, confirm and supplement their experiments We cannot subscribe, however, to the calculations and explanations given by Strouse Their experiments were carried out in the following manner The patients received test meals of the three main foodstuffs, after which short period respiratory experiments and determinations of urinary nitrogen were made When they make their calculations in these experiments, the authors take it for granted that a

1 Hagedorn, H C An Apparatus for the Graphic Recording of Oxygen Consumption and Carbon Dioxide Output, Especially Adapted for Clinical Work, *Biochem J* **18** 1301, 1924, Studies Concerning the Regulation of Blood Sugar, Physiological Papers dedicated to Professor August Krogh, Copenhagen, 1926, p 80

2 Krogh, A, and Lindhard, J The Relative Value of Fat and Carbohydrate as Sources of Muscular Energy, *Biochem J* **14** 290, 1920

3 Wang, Chi Che, Strouse, S, and Saunders, A D Metabolism of Obesity IV, Distribution of Energy Production After Food, *Arch Int Med* **36** 397 (Sept) 1925

certain amount of nitrogen excreted in the urine corresponds to a certain amount of protein combusted, and from the nonprotein quotient they calculate how much fat and carbohydrate has been combusted during the corresponding period. We are, however, of the opinion that this treatment of the excellent and important experimental results is not justified. First, we cannot take it for granted that a given amount of protein has been combusted when the corresponding amount of nitrogen has been excreted, for this only shows that the protein has been deamidized while the rest of the molecule may be retained in the organism and contain large amounts of energy. It is not a theoretical conception, but it is a well established fact that carbon is retained as glycogen after the ingestion of large amounts of meat (Williams, Rice and Lusk,⁴ experiments on dogs). Another objection is that the nonprotein quotient cannot be regarded as a definite expression for the combustion of fat and carbohydrate, this is only possible when no anabolic processes take place. We must refer to the article by Krogh and Lindhard, the far-reaching results of whose work do not as yet seem to have been given sufficient attention. Strouse and his co-workers believe that they have shown that obese people combust less fat after meals than normal persons, according to their method of calculation, this means that they have found a greater rise of the quotient after meals in obese than in normal persons. This is just what was to be expected when a transformation of carbohydrate into fat takes place to a greater extent than in normal persons.

Our experiments were undertaken with thirty obese patients (four men, twenty-six women) and sixteen normal persons (five men, eleven women). Further, we added from Krogh and Lindhard's paper the results obtained in four normal men who were examined after being on a diet similar to ours (the results for these four experiments are given in table 1). In making the calculation of the normal weights, the tables of the American life insurance companies (quoted from Joslin⁵) were employed. Compared with this, the normal persons had a weight of between -14 and $+13$ per cent, and on an average -1.5 per cent. The obese patients had an overweight of between 9.2 and 11 per cent, an average of 44 per cent. The objection may be raised that one of the normal persons had greater overweight than one of the obese persons. The explanation lies in the fact that the degree of overweight is not an absolutely correct expression of the degree of obesity. Hence we have considered it justifiable to let the judgment of the observer be determining, and not to alter this on account of the result of the calculation of the overweight arrived at later. Besides, this is unimportant for the final result.

4 Lusk, G. Science of Nutrition, Philadelphia, 1921, p. 226

5 Joslin, E. P. Treatment of Diabetes Mellitus, London, 1924, p. 761

TABLE 1—General Table of Experiments

Obese Patients										
Exp No	Subject	Sex*	Age	Height	Weight	Predicted Metab- olism (Du Bois — 5%)*	Ob- served Metab- olism	Percent- age of Devia- tion	Respira- tory Quo- tient	Per- centage Over weight
H J 1	A H	♀	48	159	121	1 22	1 42 1 45	+16	0 69 0 70	92
H J 2	O A N	♀	22	156	81	1 06	1 04 1 11	0	1 10 1 11	45
H J 3	B	♀	29	165	88	1 13	1 02 0 96	—14	0 84 0 82	44
H-J 4	L R P	♀	58	146	97	1 02	1 13 1 14	+11	0 76 0 76	67
H J 5	R S	♀	12	127	39 7	0 94†	0 84 0 88	— 8	0 84 0 81	
H-J 6	H K	♂	35	176	118	1 58	1 74 1 80	+12	0 84 0 81	55
H J 7	H L	♀	41	163	114	1 22	1 08 1 05	—13	0 76 0 77	81
H J 8	E J	♀	31	162	98	1 15	1 18 1 17	+ 2	0 76 0 75	63
H J 9	M N	♀	35	170	91	1 15	1 12 1 17	0	0 80 0 82	38
H-J 10	Y W	♀	38	160	97	1 13	1 17 1 15	+ 2	0 76 0 76	62
H 5	A L F S	♀	23	174	94	1 23	1 16 1 16	— 6	0 86 0 86	42
H 9	L S	♀	56	166	88	1 08	1 05 1 07	— 2	0 96 0 95	26
H 11	V J	♀	49	162	88	1 07†	1 14 1 22§	+10	0 74 0 77	35
H 13	A J H	♀	59	169	90	1 13#	1 08 1 10	— 4	0 77 0 80	34
H 18	Pa	♀	52	163	115	1 22	1 19 1 13	— 5	0 85 0 84	69
H 24	S	♀	26	158	80	1 06	1 12 1 16	+ 8	0 81 0 82	46
H 26	T	♀	43	153	90	1 05	1 30 1 26	+22	0 79 0 80	55
H 29	Pe	♀	29	155	78	1 02	1 10 1 14	+10	0 78 0 77	45
H 31	K J	♀	46	163	78	1 02	1 00 0 94	— 5	0 87 0 84	15
H 35	L	♀	47	160	98	1 16	1 32 1 32	+14	0 78 0 79	56
H 37	E D	♀	40	161	70	0 98	1 01 1 00	+ 2	0 91 0 92	11
H 40	P J J	♂	43	168	97	1 28	1 22 1 28	— 2	0 89 0 92	43
H 43	L M	♀	37	160	87	1 08	1 21 1 15	+ 9	0 87 0 84	45
H 45	M J	♀	15	159	78	1 18	1 04 1 06	—11	0 82 0 84	47
H 51	K M J	♀	58	163	117	1 19	1 19 1 23	0	0 77 0 80	70
H 53	Jø	♀	49	155	76	0 99	1 00 1 04	+ 3	0 79 0 80	27
H 58	Sv	♀	31	167	91	1 14	1 16 1 17	+ 2	0 85 0 84	45
H 60	N	♂	48	165	111	1 30	1 31 1 29	0	0 73 0 76	66
Hg 144	H C H	♂	36	187	110	1 39	1 22 1 27	—11	0 92 0 93	28
Hg 173	A F	♀	36	162	84	1 10	1 23 1 26	+13	0 87 0 87	38

* Du Bois' standard —5 per cent is used according to A Krogh (Boston M & S J 189
313, 1923)

† In this column ♂ indicates male, ♀, female

‡ Benedict's tables

§ Three days carbohydrate diet

¶ Experiment somewhat dubious

Three days carbohydrate diet (second day, R Q 0 731, 0 735)

TABLE 1—General Table of Experiments—Continued

Exp No	Subject	Sex	Age	Height	Weight	Normals		Percent- age of Devia- tion	Respira- tory Quo- tient	Per- centage Over- weight
						Predicted Metab- olism (Du Bois — 5%)	Ob- served Metab- olism			
H-J I	P J	♂	20	182	78	1 26	1 23 1 14	— 6	0 92 0 92	+10
H-J IV	N A	♂	23	175	70	1 16	1 14 1 09	— 4	0 91¶ 0 90	+ 3
H 3	N	♂	21	173	59	1 08	1 16 1 18	+ 8	0 95 0 94	—11
H 22	Kn	♂	21	172	63	1 09	1 12 1 04	— 1	0 82** 0 83	— 1
H 63	B H	♀	20	152	57	0 90	0 98 0 97	+ 8	0 88 0 88	+12
H 64	A H	♀	20	160	60	0 96	1 14 1 14	+10††	0 82 0 82	+ 9
H 65	Chr	♀	19	160	62	0 99	0 97 1 02	0	0 86 0 84	+13
Hg 63	k H	♂	20	189	80	1 32	1 31 1 31	— 1	0 85‡‡ 0 84	+ 7
Hg 131	S	♀	31	176	61	1 00	0 90 0 91	—10	0 84 0 83	—10
Hg 145	H N	♀	19	169	66	1 07	1 04 1 04	— 3	0 86 0 87	+ 8
Hg 150	I L	♀	26	169	61	0 99	1 02 1 01	+ 2	0 85 0 84	— 3
Hg 174	R M	♀	21	174	61	1 02	1 06 1 08	+ 5	0 73 0 73	— 6
Hg 178	M H	♀	37	161	60	0 92	0 97 0 95	+ 4	0 91 0 90	0
Hg 179	K J	♀	20	169	58	0 97	0 99 0 99	+ 2	0 88 0 88	0
Hg 180	B O	♀	21	169	54	0 96	1 04 1 07	+ 9	0 84 0 84	—13
Hg 181	M R	♀	19	176	66	1 09	0 99 1 02	— 9	0 75 0 76	+ 3
A K, p 306, Feb 12		♂	42	176	67	1 10	1 04 1 05	— 5	0 88 0 87	—10
R E, p 306, June 6		♂	25	170	64	1 09	1 34 1 31	+29	0 93 0 90	— 3
O H, p 316, May 14		♂	23	179	80	1 27	1 46 1 40	+13	0 95§§ 0 95	+14
A M N, p 323, Feb 2		♂	24	175	63	1 10	1 22 1 17	+ 8	0 90 0 88	+ 9

** One day carbohydrate diet (2 days R Q 0 811, 0 849)

¶ Three days carbohydrate diet (2 days R Q 0 882)

†† Eleven a m after three-fourths hour of repose At work from 8 30 a m

‡‡ Four days carbohydrate diet

§§ Three days carbohydrate diet (2 days R Q 0 92, 0 96)

Part of the obese people were patients in the hospital and part were private patients. These patients were examined without having received any previous treatment. They took the following diet for two days before the experiment, and were told to eat plentifully.

Breakfast Toast with marmalade or honey. Coffee or tea with sugar (no cream). Rice porridge or oatmeal porridge. Boiled fruit.

Lunch Macaroni or boiled rice with tomato sauce (with a little cheese). One egg. Potatoes (boiled, roasted). Sauce without butter (or any kind of fat). Bread with marmalade or honey.

Afternoon meal Bananas, oranges, apples or pears, buttermilk

Dinner Rice porridge with fruit juice 100 Gm boiled cod or plaice with 10 Gm melted butter Potatoes Fruits, raw or boiled (nuts not to be eaten)

Supper Rice or barley porridge with fruit juice Bread with marmalade or honey Figs, dates and other fruits (except nuts) Tea, buttermilk

Flour, meal, fruits (except nuts), vegetables and sweets can be eaten as desired at any time of the day Fish, eggs and butter must be taken only in the amounts prescribed

The determination of the respiratory metabolism was made in the morning or early in the forenoon, before the patient had had his breakfast and after complete rest for from one-half to one hour All the persons who were examined breathed with a mouthpiece and nose-clip

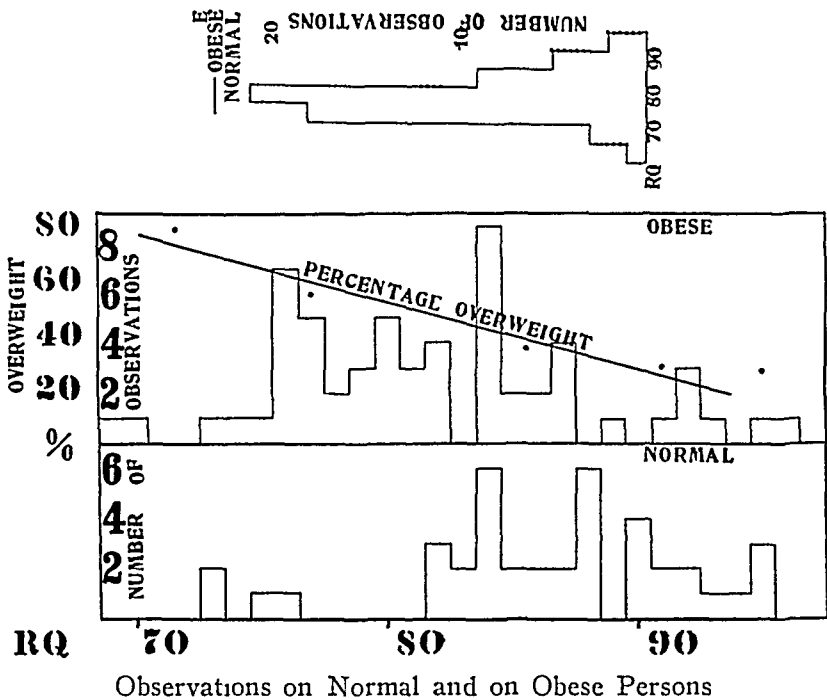
TABLE 2—Results of Experiments on Normal Persons and on Obese Patients*

			Respiratory Quotient		Mean
			0.700-0.825	0.825-0.900	
Normal Persons					
Total number of single determinations	40	Number of single determinations	5 13%	35 87%	0.861 ± 0.009
Obese Patients					
Total number of single determinations	58	Number of single determinations	34 59%	24 41%	0.816 ± 0.008
Difference					0.045 ± 0.012
Average overweight			53%	36%	

* The experiments on normal persons and obese patients are divided into two groups, the one comprising the experiments in which the quotients are higher than 0.825, the other comprising the quotients lower than 0.825, the average overweight for the patients in each group is given

into the apparatus at least once before the determination. This is important, as nervousness and uneasiness may otherwise make the results inaccurate. The experiments were undertaken with Hagedorn's apparatus, which graphically records oxygen consumption and carbon dioxide production. Double determinations (each lasting ten minutes) were made on every patient. All experiments in which the curves were not straight were rejected, as this signifies uneven ventilation. Experiments in which the double determinations showed a greater difference between the quotients than 0.03 were also rejected. One set of double determinations was rejected in which the quotients of 1.1 and 1.12 were found. Probably this patient had received a meal by mistake a short time before the examination. Even if this experiment is taken into consideration, it does not alter the final result of the series. A number of both patients and normal persons were examined several times. Eight of the obese patients were examined after having been on the carbohydrate diet one day and two days. The average quotient after one day was 0.843 and after two days 0.843. Five were examined after two

days and three days on a carbohydrate diet. The average quotient was 0.814 and 0.807, respectively. No significant difference was found for normal persons that had been on the diet for one, two or three days. In table 1 are given the experimental results after a carbohydrate diet generally for two days. The figures given in this table have been employed for the succeeding calculations. In table 2 the averages for the experiments on the obese patients and on the normal subjects have been given, together with the mean error of the two series. As will easily be seen, a real difference is found, so that obese persons on an average have a lower quotient on a carbohydrate diet than normal persons.



In the chart, the number of cases observed for each quotient is plotted. The upper part of the chart represents the results for the obese patients, the lower part represents the observations for normal persons. The percentage overweight for the obese is also given. It is remarkable to note that the phenomenon of the low respiratory quotient is related to the percentage overweight in such a manner that the greater the percentage overweight, the lower the quotient observed. For the normal persons the weight was also brought into relation with the quotient, but no dependence was found.

As will be seen, there are two normal persons with a low respiratory quotient. With all the reservations necessary when so few observations are taken into consideration, we may suggest that these persons may be disposed to obesity. The two women were 18 and 20 years old. It does not seem unreasonable in view of the frequency of obesity to suppose that the anomaly ultimately resulting in obesity may be found in young persons who apparently are still normal.

The relation shown between the percentage overweight and the respiratory quotient on carbohydrate diet shows that the obesity is in some way or other connected with qualitative anomalies in the metabolism, but this does not exclude the possibility that in some types of obesity the low respiratory quotient is not present. If such types are present in our material, they have escaped recognition, since, on account of the large individual differences, we have been obliged to combine and treat the material in groups.

SUMMARY

A number of normal and obese persons have been examined by determining their respiratory quotients by means of a self-recording apparatus after they had for two days taken a diet consisting chiefly of carbohydrates. By this method a real difference between the mean respiratory quotient in obese and in normal persons has been found, the respiratory quotient in obese patients being lower than that in normal persons. The results confirm the hypothesis that obesity is due to a qualitative anomaly in metabolism, i. e., an abnormally increased transformation of carbohydrate into fat. It has been shown that a relation between the percentage overweight and the respiratory quotient in obese subjects is found, patients with great overweight having a particularly low respiratory quotient, while the patients with less overweight have a respiratory quotient which is nearer or within the normal zone.

The experiments have been undertaken partly in the third medical department of the City Hospital of Copenhagen and partly in the private laboratory of Dr. Hagedorn.

BLOOD PRESSURE OF FOREIGNERS IN CHINA¹

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Hypertension, unassociated with cardiac or renal disease, so common in other countries, is uncommon in China. Attention has been called to this by Cadbury,¹ Cruickshank,² Kilborn³ and others, who have also shown that the average blood pressure of the Chinese is lower than the average for persons in other countries. In the Hunan-Yale Hospital, of more than 4,000 cases in the medical service department during the past four years, there has been only one diagnosed as essential hypertension, and, including the cases of nephritis and cardiac disease, not more than twenty with blood pressures over 160. During two years, 1918 and 1919, of 4,940 patients in the medical service of the Peter Bent Brigham Hospital,⁴ Boston, there were 236 cases of essential hypertension and 146 cases of chronic nephritis with hypertension.

It has been my impression and that of others on our staff that less hypertension is seen among the Occidentals living in China, and that the average blood pressure of foreigners is lower than the average usually accepted as normal. Little information on this point has been found in the journals and textbooks on tropical medicine.

Studies on the blood pressure in India⁵ seem to show that the average systolic blood pressure of the Hindus is about 100 millimeters of mercury, while that of the Europeans in Bengal is from 115 to 130 mm. There are conflicting reports from the Philippines. Musgrave and Sison,⁶ in 1910, and Concepcion and Bulatao,⁷ in 1916, found that the blood pressure of the Filipinos was lower than the average given for Americans and Europeans, and that the blood pressure of Americans living in the Philippines was about the same as that of the Filipinos.

¹ From the Department of Medicine, Hunan-Yale Hospital, Changsha, China.

² Read before the Section of Medicine at the Conference of the China Medical Association, Peking, China, Sept. 1-8, 1926.

1 Cadbury, W. W. The Blood Pressure of Cantonese Students, *China M. J.* **37** 823 (Oct.) 1923.

2 Cruickshank, E. W. H. Physiological Standards in North China, *China M. J.* **37** 1 (Dec.) 1923.

3 Kilborn, L. G. The Blood Pressure of Szechuenese Students, *China M. J.* **40** 1 (Jan.) 1926.

4 Hospital Rep. Peter Bent Brigham Hospital, 1918 and 1919.

5 McCay, D., quoted by Cadbury (footnote 1).

6 Musgrave, W. E., and Sison, A. G. Blood Pressure in the Tropics, *Philippine J. Sc.* **5** 325 (Aug.) 1910.

7 Concepcion, I., and Bulatao, E. Blood Pressure of the Filipinos, *Philippine J. Sc.* **11** 135 (May) 1916.

Chamberlain,⁸ however, in 1912, at the head of an army board appointed to investigate tropical diseases in the Philippines, during a careful study of more than 6,000 observations on the blood pressure of 1,042 American soldiers and of more than 500 observations on 386 Filipino soldiers, concluded that, "The blood pressure of Americans residing in the Philippines differs but little if any from the average at home" (average 115 mm for from 18 to 30 years of age and 118 for over 30), and that there was not a tendency for the blood pressure to rise or fall with increasing length of residence, up to three years, the limit of their study. He found that the average pressure for the Filipinos was "practically identical with that for the group of white men" (116 mm for from 15 to 40 years of age). The textbooks⁹ refer only to Chamberlain's work in their brief references to blood pressure in discussing the effects of the tropics on the white race.

In 1923 the Health Committee of the Yale Mission introduced a uniform system of medical examinations for candidates before coming to China and annual examinations thereafter. In the four years' records now available, there are two points that have impressed the members of this committee: first, that the average systolic blood pressure for the whole group is lower than the usual average for Americans, and second, that many show a definite drop in blood pressure in China as compared with the pressure recorded in America.

From the hospital and health records my co-workers and I obtained the blood pressure of 120 men and women, all foreigners—a few Europeans, but mostly Americans. Persons with diseases which were likely to affect the blood pressure were not included. The foreign community of Changsha is small, which has made it difficult to get a larger series. The blood pressure of the men and women was almost identical, an average of 112 mm for sixty-three women and 113 mm for fifty-seven men. The distribution was approximately the same, so the results for both men and women are included in the same table.

The blood pressure of 278 apparently healthy local Chinese was obtained from the Hunan-Yale Hospital and Dispensary records for comparison.

In 1923, Alvarez¹⁰ reported the blood pressures in nearly 15,000 American men and women. His results are included with ours in table 1.

8 Chamberlain, W. P. A Study of the Systolic Blood Pressure and the Pulse Rate of Healthy Adult Males in the Philippines, *Philippine J. Sc.* **6** 467 (Dec.) 1911.

9 Castellani and Chalmers. *Manual of Tropical Medicine*, 1919. Byam and Archibald. *The Practice of Medicine in the Tropics*, 1921.

10 Alvarez, W. C. Blood Pressures in Fifteen Thousand University Freshmen, *Arch. Int. Med.* **32** 17 (July) 1923.

In table 2 are shown the results for a slightly different group including Americans and Filipinos in the Philippine Islands, as reported by Musgrave and Sison and by Chamberlain. Cadbury's figures for Cantonese students are also given in this table.

TABLE 1—*Percentage Distribution of a Series of Systolic Blood Pressures of Groups of Foreigners and Chinese in Changsha Compared with Averages for Americans*

	Blood Pressures									Number Examined
	80 to 89	90 to 99	100 to 109	110 to 119	120 to 129	130 to 139	140 to 149	150 to 159	160 to 169+	
Foreigners (Changsha) men and women	2%	19%	30%	23%	15%	5%	3%	1%	2%	120
Chinese (Changsha)	3%	18%	32%	29%	10%	3%	3%	2%	1%	273
Women U S A (Alvarez) ¹⁰	(0-3%)	3%	18%	36%	29%	10%	2%	1%	1%	9,000—
Men, U S A (Alvarez)	—	1%	3%	18%	31%	28%	13%	5%	3%	6,000
Americans men and women (Alvarez)	—	2%	12%	29%	30%	16%	6%	3%	2%	15,000—

TABLE 2—*Percentage Distribution of Blood Pressures of Groups in the Philippines and of Some Cantonese Students*

	Blood Pressure									Number Examined
	71 to 80	81 to 90	91 to 100	101 to 110	111 to 120	121 to 130	131 to 140	141 to 150	151 to and Over	
U S soldiers (Philippines) ⁸	—	—	5%	29%	37%	21%	5%	2%	1%	992
Filipinos ⁸ (soldiers)	—	1%	7%	26%	34%	19%	7%	2%	4%	366
Foreigners ⁸ (Philippines)	—	—	1%	17%	34%	23%	13%	7%	2%	97
Cantonese students ¹ (over 20 years)	4%	12%	38%	22%	16%	7%	—	—	—	?

TABLE 3—*The Average Systolic Blood Pressures for Different Racial Groups as Given by Different Observers*

Groups	Reported by	Number Examined	Average Systolic Pressure
Philippines			
Filipino soldiers	Chamberlain	366	115 - 116
Filipino civilians	Concepcion	697	115.6
American soldiers	Chamberlain	1,042	115 - 118
India			
Hindus	McCaJ	500 ?	90 - 105
Europeans	McCaJ	?	115 - 130
America			
Women	Alvarez	9,000	117.3 ±10.8
Men	Alvarez	6,000	128.9 ±13.5
Men	Woley (J A M A 55: 121 [July 9] 1910)	1,000	127.5
China			
Cantonese students	Cadbury	700	101
Szechuan students	Kilborn	700	111
Hunan students	Kao (Nat M J China 8: 101 [June] 1922)	261	114.5
Hunan, adults	Foster	278	111 ±10.6
Foreigners, Hunan	Foster	120	112 ±14.7

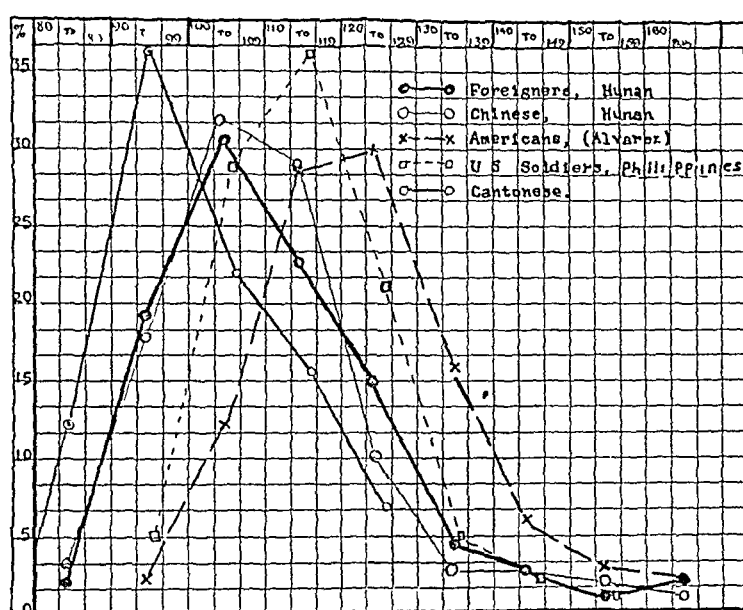
The average blood pressures as given by different observers for different racial groups of all ages are given in table 3.

A comparison of the various reported series, chart 1, seems to show that for this small number, at least, the average blood pressure of the foreigners in Changsha, as in the Philippines, is definitely lower than

the figures set by Alvarez as normal for Americans, and that the average for the foreigners in Changsha is almost identical with that of the local Chinese

Data of thirty-four men and women, with blood pressures recorded in America and again a year or more later in China are shown in table 4. Eight do not show any change, two show an increase in pressure, but the remainder show a drop of from 10 to 40 mm. of mercury after living a year or more in China.

There are several persons with rather striking changes. R. A. had a blood pressure of from 140 to 145 for several years in America, it dropped to 128 and 120 during four years in China. W. H. had been



Comparative curves of some blood pressures given in tables 2 and 3

refused life insurance several years before because of high blood pressure, although it was usually from about 135 to 140. This dropped to 125 and 108 in two years in China. L. F., whose pressure was always around from 118 to 120, dropped each year in China—112, 102, 95 and 88—without subjective symptoms of any weakness or any physical signs of hypotension. A Chinese woman physician (S. C., the report not included in the foregoing tables), who was born in Hawaii but who had always lived in the United States, had a blood pressure of 120 in 1923 before coming to China. It dropped to 115 and to 88 this year. I have the reports of only two taken before, during and after furlough. The blood pressure of E. H. was 116 in 1923 in China, 140 in November in America and 128 the following year in China, that of F. H. was 120 in China, 130 in America and 108 for the following two years in Changsha.

A similar series of records of the blood pressure of forty members of the Peking Union Medical College staff was obtained ¹¹ (table 5). In this series, twelve do not show any definite change, or less than 5 mm up or down, only three show an increase, while twenty-five show a decrease. The average for the group taken in Peking is 9 mm less than in America (118 in the United States, 109 in Peking). In the Changsha series there was a difference of from 8 to 14 mm (121 in the United States, and 113 or 107 in Changsha, depending on whether the maximum or minimum China record was taken).

TABLE 4—*Blood Pressures of Thirty-Three Adult Americans Taken in Routine Physical Examinations in America and Again After a Year or More in Central China, Two-Thirds Show a Definite Drop in Blood Pressure*

Name	Age	Sex	Years in China	Height		Weight	Blood Pressure in U S A	Blood Pressure in China	Change in Blood Pressure
				Ft	In				
R A	34	M	4	6		167	140	128 120 120	-20
H B	25	M	1	5	5	145	135	118	-17
S B	24	F	1	5	3	115	114	100	-14
N B	23	F	2	5	3	120	130	110, 90	-40
W B	24	M	1	6		140	116	80	-36
J B	43	M	10	5	11	140	104	94, 98	-6
S C	22	M	1	5	6	147	118	116	0
L F	34	F	4	5	4	120	118	110, 102, 95, 88	-30
J F	34	M	6	5	9	160	110-118	118, 110	0
M F	21	M	1	5	10	170	122	115	-7
L G	26	F	1	5		126	120	108	-12
C G	25	F	2	5	5	125	125	108 105	-20
P G	30	M	3	5	9	160	120	120, 102, 100	-20
R G	30	F	3	5	3	104	102	112, 118	+16
E H	40	M	16	5	11	205	140	116, 128	-12
F H	40	F	16	5	6	134	130	108, 108	-22
W H	50	M	3	6		204	135	125, 108	-27
O K	25	M	3	5	9	200	130	140, 130, 125	0
E K	22	F	2	5	2	120	120	105, 105	-15
J L	25	F	1	5	1	112	114	122 112	0
S M	22	M	1	5	10	147	120	100	-20
M M	28	F	2	5	3	120	116	116, 100	-16
J N	28	F	2	5	8	160	132	136, 122	-10
P P	24	M	2	6		156	112	120, 120	+ 8
R P	36	M	10	5	7	126	120	116 108 95	-25
M P	35	F	10	5	4	122	120	100, 96, 92	-28
H R	30	M	3	5	10	200	120	124, 124	0
K R	22	M	1	5	9	128	106	104	0
D S	24	M	2	6		165	122	124	0
T V	23	M	1	5	7	128	110	110	0
C W	25	M	2	5	10	140	112	92, 100	-12
O W	30	F	5	5	4	135	118	105, 95	-23
A W	22	M	1	5	10	146	132	112	-20

The figures are presented for what they are worth. Most were single observations, but were taken in routine medical work, and when possible they have been verified. The records were made with Tycos, aneroid and Baumanometer mercury instruments using a 12.5 cm band. The auscultatory method was used as a routine. Some slight variations were noted in checking up the different instruments and observers. The

¹¹ Dr Otto Willner, in charge of the Department of Staff Health of the Peking Union Medical College, through whose courtesy the figures in table 5 were obtained, asserts that the blood pressure of foreigners seen in practice in Peking tends to average around 110 or lower, rather than around 120, which is considered normal in the West.

records were taken when the subject was sitting, some were taken in the afternoon, others in the forenoon, most were taken during the months of April and May. There did not seem to be any seasonal variation.

COMMENT

One does not know how to comment on the significance of such a small series, which would have a large probable error. How different would a larger series be? Do these same changes in blood pressure occur in all parts of China?

TABLE 5—*Blood Pressure Records of Forty Foreigners Taken Before and After Coming to China*

Name	Age	Sex	Blood Pressure in U S A	Blood Pressure in China	Change in Blood Pressure
A	25	M	122	108	-14
B	31	F	110	106	-4
C	35	F	132	110	-22
C	33	M	120	118	-2
C	36	F	120	100	-20
D	52	M	112	114	+2
D	36	F	120	120	0
E	39	M	120	108	-12
F	35	M	128	110	-18
F	33	F	120	110	-10
F	?	F	120	110	-10
F	31	M	118	125	+7
G	36	F	106	102	-4
G	39	F	118	120	+2
G	33	F	115	110	-5
G	30	F	103	100	-3
G	33	F	115	105	-10
H	28	F	118	110	-8
H	30	F	130	110	-20
H	44	M	122	118	-4
J	?	F	108	112	+4
K	34	M	120	114	-6
K	29	M	120	110	-10
K	29	F	125	114	-11
K	28	F	100	84	-16
K	24	M	100	106	+6
K	39	M	135	108	-27
L	?	M	115	120	+5
L	26	F	118	90	-28
M	32	F	115	112	-3
P	32	F	124	102	-22
S	32	M	112	105	-7
S	42	F	121	130-114	0
T	35	M	130	115	-15
T	28	F	130	110	-20
T	?	F	118	118	0
V	36	M	110	92	-18
V	42	M	125	108	-17
W	44	M	106	106	0
W	45	F	120	98	-22

* Over 60 per cent have a lower blood pressure in China. Only three show an increase.

The comparative hypotension itself does not seem important, for even those with blood pressures in the eighties and nineties do not complain of symptoms. It apparently does not have any relation to ill health, change of diet, shorter hours of work or exercise, amount of sleep or lack of nervous tension or strain, but it may have some relation to the feeling some have expressed of lack of energy and capacity for work in China as compared with their feeling when in the "States."

The significance of this variation seems to be that an answer to this question might give some clue to the etiology and possible treatment of

the other and more important side of this same problem, that is, hypertension. An explanation of essential hypertension which will withstand rigid criticism has not yet been offered. Many cases of hypotension are equally unexplained. A solution of these problems might be found if the factors of difference in the lives of persons living in China and those living in Western countries could be analyzed.

Many factors have been suggested from time to time to explain the low blood pressure of the Chinese. (1) smaller stature and lighter weight, (2) decreased capacity for muscular effort with resulting decrease in muscular tone, (3) some racial endocrine differences, (4) diet, largely vegetable, low in protein and salt, (5) climate, which lowers vasomotor tone, especially of the splanchnic and peripheral vessels, or which, by the increased secretions from the skin, causes lowered surface tension or possibly causes some variations in the volume and viscosity of the blood, and (6) the simplicity of life in China and the absence of nervous strain.

None of these theories has been proved. Cadbury feels that possibly (1) and probably (4) and (5) are real factors. Musgrave and Sison lay most emphasis on (5). If it is true that the blood pressure of Chinese and foreigners is influenced alike, it would seem to rule out the question of physical stature or development and of the endocrines. So far as protein intake is concerned, there does not seem to be a great difference in the diet of foreigners living in China and at home. As to climate, Changsha is not in the tropics. The mean temperature is about that of Alabama and Mississippi, and any unusual absence of hypertension in those states has not been reported. Peking is in about the same latitude as New York City. Could it be that there is some subconscious adjustment to the unhurried life of the East that lowers the general tone?

One case of essential hypertension in a Chinese is of interest in connection with the question of etiology. Miss T, a supervisor in the Nursing School, aged 38, had completed her education in America and had returned to China in 1922. In November, 1925, after three years in north China, she came to us complaining of persistent headaches and insomnia. The results of the examination of the heart, eyes, sinuses and other organs, as well as urinalysis, were normal. Her blood pressure was 180 systolic, and 110 diastolic. Roentgenograms of the teeth, sinuses and heart were normal, and there was normal renal function. She had an intensely nervous temperament and seemed more like a Westerner than a Chinese in her habits and attitudes. On enforced rest and limitation of duties, her blood pressure dropped later to 130 and 135. Was it that the nervous tension was responsible for her hypertension or was the high blood pressure the cause of her highstrung temperament?

The foregoing figures and observations are presented to call attention to some facts which should receive further investigation. At present there does not seem to be any real answer as to why there is such an absence of hypertension in China, or any adequate explanation for the lower blood pressure that seems to exist.¹²

SUMMARY

1 The blood pressure of the Chinese has been shown to be lower than the usual averages, and hypertension is rare.

2 The blood pressure of a series of Occidentals living in China shows that the average for foreigners is about the same as that of the local Chinese, and that the blood pressure of the majority of persons studied was lower in China than in America.

3 An analysis of unknown factors responsible for this comparative hypotension may give some clue as to the cause of hypertension in other countries.

12 In a recent communication, Mr. E. F. Harris, manager of the North China Division of the Sun Life Insurance Company, Shanghai, has sent the results of the blood pressures of about 1,000 policy holders, Chinese and foreigners, for analysis. He makes the following comment: "In my opinion our experience does not bear out the deductions which you mention. In our experience the blood pressure of the Chinese is considerably lower than the blood pressure of the Caucasian races. The blood pressure of the white races, i. e., European and Americans, in China, is, however, in our experience just the same as the blood pressure of such races in Europe and America. We also are of the opinion that hypertension in foreigners is just as common in China as in Western countries, but that hypertension is rare in the Chinese."

THE PATHOGENIC RÔLE OF TRICHOCEPHALUS DISPAR (TRICHURIS TRICHIURA)²

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It seems to be generally ignored that *Trichocephalus dispar*, one of the intestinal parasites most common in man, is a parasite of pathologic importance. The majority of textbooks give few data concerning the pathologic changes which may be produced by this organism, some authors treat the matter as if it were not of importance, saying that the organism is harmless, without offering any proof for such an affirmation.

This lack of attention to *Trichocephalus dispar* is probably due to its frequent association with the hookworm, the study of which has been such an attractive theme in biology that any symptoms due to the former were accepted as a result of the latter.

My purpose is to call attention to the clinical importance of *Trichocephalus dispar* and to review the facts obtained by various workers, in the hope that this may lead to further study of this important human parasite.

METHODS OF STUDY

Preservation of Helminths (Method of Leyer) —The worms are placed in a test tube to which is added sufficient physiologic sodium chloride, and shaken well in order to cleanse the mouth and other parts of the worms of earthy material. The worms are then dropped into boiling alcohol (70 per cent), *Trichocephali* stretch out and die in a characteristic position. They are then transferred to 96 per cent alcohol for thirty minutes. They are immediately cleared in white creosote until transparent and the histologic details of the different organs can be observed. Within twenty-four hours the creosote restores the normal contour and any irregularities caused by the alcohol. After the examination in creosote the worms are preserved in 70 per cent alcohol.

Examination of Ova —From 5 to 10 Gm of feces are diluted with an equal amount of a saturated solution of common salt and beaten well in order to free the eggs, which float to the surface of the mixture. A slide is applied to the surface for five minutes in order that the eggs may stick to the glass. It is turned over by a quick movement, a cover-slip applied, and a microscopic examination made. As the eggs of *Trichocephalus* are few in comparison with those of *Uncinaria*, this method will render possible a positive diagnosis in many cases when the ordinary methods of examination would be negative.

Unlike *Oryzias vermicularis*, the eggs of *Trichocephalus* do not hatch out in the intestine of its immediate host, but are eliminated with the feces. In the soil the eggs begin their development, the embryos form slowly in the periphery of the egg, and arrive at maturation in from six to ten months. Owing to the thick outer covering of the egg, the embryo can resist ice, intense heat, digestion or putrefaction. Davarine¹ succeeded in preserving embryos of *Trichocephalus* in encysted form for more than five years. Ingested by a warm-blooded host they develop rapidly, provided they have remained in damp earth or water for at least a month before passing to the host. Before this interval the ova will pass through the intestinal tract without hatching.

² From the University of Madrid Faculty of Medicine.

¹ Brumpt, E. *Precis de Parasitologie*, Paris, 1923.

GEOGRAPHIC DISTRIBUTION

Trichocephalus dispar is a nematode of cosmopolitan distribution. It is well adapted to an environment of wet and cold earth, such as is encountered in mines and forests. Statistics show that the number of cases of disease caused by it varies, as is shown in table 1.

TABLE 1—Percentage of Cases Caused by *Trichocephalus Dispar* in Various Localities

Autopsies	Infected With <i>Trichocephalus</i> , per Cent	Investigator
Munich	9	Braun
Kiel	31	Braun
Gottingen	46	Braun
Basle	23	Braun
Paris	50	Richard
London	65	Henderson
Dublin	82	Costello
Genoa	86	Martinelli
Madrid	6	De Buen
Barranquilla	62	Núñez
Tela (Honduras)	51	Clark (Thirteenth Annual Report, United Fruit Company Medical Department, 1924)
Coprologic Examinations		
Brazil	82	Serpa
Colombia	47	Cadena (Repert de med y chir, Bogota, 1924)
Colombia	41	Núñez
Honduras	29	Clark
Mexico	38	Sarmiento
Japan	65	Fukawa
Northern China	90	Young
Philippines	45	Ortega
Siam	28	Horton
Nigeria	37	Erskine
Argentina	14	Castej (Prensa med argent May 30, 1925)
Madagascar	45	Blanchard
Scotland (miners)	80	MacPherson
France (miners)	78	Brumpt
Spain	12	Núñez
Texas	25	Gonzalez

In a study of 1,336 examinations of feces of laborers in the Colombia Syndicate Hospital, Barranquilla, Colombia, I found 92 per cent positive for intestinal parasites. Of the 1,336 cases studied, *Trichocephalus dispar* was present alone, or in association with other parasites, in 41 per cent.

An interesting feature of table 2 is the negligible percentage of tapeworms. This is due to the Spanish-American custom of cooking thoroughly all meats that are eaten.

TRANSMISSION OF INFECTION

Grassi was the first to work out the method of transmission of *Trichocephalus*. Among other studies, he showed that if eggs of *Trichocephalus dispar* are injected into a human being, characteristic eggs of the parasite appear in the feces of the subject on the twenty-seventh day.

In order to extend the work of Gordon² carried out in suckling pigs, I injected a suspension of feces containing eggs of *Trichocephalus depressusculus* (the dog *Trichocephalus*) into the subcutaneous tissue of a dog 6 weeks of age, which on repeated previous examinations had been found free from infestation with *Trichocephalus*. Characteristic eggs presented themselves in the feces within five weeks and persisted for several months.

Howard³ observed eggs of *Trichocephalus* in the feces of an infant aged 14 days, and concluded that it was a case of intra-uterine infection.

TABLE 2—*Appearance of Trichocephalus Dispar Alone or With Other Parasites in 1,336 Cases*

Ancylostomas alone (including Uncinaria)	202
Ascaris lumbricoides	142
Trichocephalus dispar	160
Ameba histolytica	48
Strongyloides intestinales	8
Cereomonas, Trichomonas and Lamblia intestinalis	6
Ancylostomas and Lumbricoides	110
Ancylostomas and Trichocephalus dispar	104
Ancylostomas and Strongyloides	23
Ancylostomas and amebas	20
Ancylostomas and Trichomonas	6
Ancylostomas and Balantidium coli	2
Lumbricoides and Trichocephalus dispar	46
Lumbricoides and Strongyloides	6
Lumbricoides and amebas	6
Trichocephalus dispar and Strongyloides	8
Trichocephalus and amebas	10
Amebas and Strongyloides	4
Ancylostomas, Lumbricoides and Trichocephalus	92
Ancylostomas, Lumbricoides and Strongyloides	4
Ancylostomas, Lumbricoides and Taenia circinata	2
Lumbricoides, Trichocephalus and Strongyloides	18
Lumbricoides, Trichocephalus and Trichomonas	8
Lumbricoides, Trichocephalus and amebas	4
Trichocephalus, Strongyloides and amebas	2
Ancylostomas, Lumbricoides Trichocephalus and Strongyloides	30
Ancylostomas, Lumbricoides Trichocephalus and amebas	8
Ancylostomas, Lumbricoides, Strongyloides and Oxyuris vermicularis	2
Ancylostomas, Trichocephalus, amebas and Trichomonas	6
Ancylostomas, Trichocephalus, Lumbricoides, Strongyloides and Taenia circinata	2
Ancylostomas, Trichocephalus, Lumbricoides, Trichomonas, amebas	10
Ancylostomas, Trichocephalus, Lumbricoides Strongyloides and Balantidium coli	2
Ancylostomas, Trichocephalus, amebas, Lumbricoides, Trichomonas and Bilharzia	2
Negative examinations	92
Total	1,336

PATHOLOGY

Trichocephalus dispar may produce its effects on its host through various avenues, which may be well illustrated using Pittaluga's⁴ classification for parasites in general

2 Gordon, R. M. A Further Note on the Occurrence of Ankylostomes Resembling Necator Americanus Amongst Domestic Pigs in Amazonas, Ann Trop Med **17** 289 (July) 1923, Ann Rep Rockefeller Foundation, New York, 1922

3 Howard, H. H. A Case of Intrauterine Helminth Infection, S African M Quart, 1891

4 Pittaluga, G. Enfermedades de los Paises Cálidos y Parasitología General, Librería Calpe, Madrid, 1924

1 Mechanical Action

- (a) The worm perforates the mucous membrane, inserting its slender cephalic process into the submucosa or muscular coat of the intestinal wall
- (b) It may penetrate the intestinal wall and encyst in the abdominal cavity
- (c) It may reach the lungs within twenty-four hours and be found there by autopsy (G. Neshi)
- (d) With the head fixed in the intestinal wall the constant oscillatory movements of its body may originate intense reflexes through the sympathetic nervous system producing a great variety of symptoms in remote parts of the host
- (e) When it is fixed in the appendix, the peristaltic movements of the organ can carry the body of the worm out through the appendicular valve, closing it
- (f) Through perforation of the intestinal wall pathologic organisms may gain access to the abdominal cavity
- (g) The ova may serve as nuclei for calculi, especially in the appendix

2 Direct Exspoliative Action

- (a) Extraction of blood and lymph from the host

3 Indirect Exspoliative Action

- (a) Extraction of blood and lymph deprives the host of a part of his aliment

4 Toxic Action

- (a) Excretion of toxic products of metabolism which are absorbed by the host
- (b) Injection of hemolytic enzymes in the host
- (c) Injection of specific toxic proteins, as evinced by the great increase in eosinophils in the blood of the host

EOSINOPHILIA

One of the constant sequelae of *Trichocephalus* infection, as in infections by other parasites, is the presence of a decided eosinophilia. The eosinophils have a specific function in the destruction of heterogeneous animal proteins. In infection caused by *Trichocephalus*, the eosinophils show a constant increase greater than in infections due to other intestinal parasites, reaching from 30 to 40 per cent in some cases.

In order to study the comparative eosinophilia produced by different intestinal parasites, I examined the blood of 512 patients who had helminth eggs in their feces. I made the following observations:

(a) Ninety per cent had a definite eosinophilia, that is more than 4 per cent of eosinophils.

(b) The average eosinophilia in these cases was 12 per cent.

(c) In 302 cases of infections caused by *Necator americanus* and *Anchylostoma duodenale*, some associated with *Trichocephalus dispar*, and the rest with other helminths, 93 per cent demonstrated an eosinophilia, averaging 10 per cent.

(d) Of fifty-one cases of infections caused by *Ascaris lumbricoides* alone, 80 per cent revealed an eosinophilia average of 8 per cent.

(e) Forty-eight cases caused by *Trichocephalus dispar* alone, gave an eosinophilia average of 14 per cent.

The marked eosinophilia in infections caused by *Trichocephalus dispar* is of great interest, because it would seem to demonstrate that a few trichocephali are able to poison the patient in equal or greater degree than a large number of hookworms.

The following technic is useful for greater facility and precision in the study of eosinophilia. Blood is obtained with a pipet for leukocytes, and diluted 1:10 with 1 per cent (1 cc) of aqueous solution of eosin, 1 per cent (1 cc) of aqueous solution of acetone, and 10 cc of distilled water. The eosinophils are seen as brilliant red granules over a pink field.

HELMINTHIC APPENDICITIS

It was Moigagni who called attention to the tendency of *Trichocephalus dispar* to localize in the cecum and appendix. Metchnikoff (1901), before the Academy of Medicine of Paris, directed special attention to *Trichocephalus* as a frequent factor in appendicitis. This event immediately led to the study of the nematode by various investigators in all parts of the world.

Brumpt and Lucerne¹ found *Trichocephalus* in 10 per cent of appendixes of adults coming to autopsy, most frequently in association with *Oxyuris vermicularis*. Of twenty-one patients with appendicitis operated on by Oelnitz,¹ eighteen patients had eggs of *Trichocephalus* in the appendicular cavity. Roillet¹ found live trichocephali in the appendix of a patient operated on after the intensive use of thymol. De Buen,⁵ in a study of the appendixes of 100 patients who had died from various diseases, demonstrated nematodes in six cases.

I performed sixteen autopsies on laborers dying from various causes in Colombia. Ten of these showed trichocephali present. In all cases worms were present in the cecum, in two in the appendix, in four in the hepatic and splenic curvatures of the colon, in four in the sigmoid and in six in the rectum. One patient had two worms in the ileum. Some observers state that *Trichocephalus* loosens its hold on the intestinal wall within two hours after the death of the host. As the Colombian laws prohibit autopsies in less than eight hours following death, I was surprised to find four cadavers in which the worms were still attached to the mucosa.

In a review of 100 reported cases of appendicitis due to infection with *Trichocephalus dispar* and *Oxyuris vermicularis*, ten were due to infection with *Trichocephalus* alone. All ten occurred in patients under 14 years of age. One of the patients with gangrenous appendicitis died, the others survived, due, no doubt, to the fact that all were operated on early.

5 De Buen, S. Estudio Parasitologico de Cien Apendices Humanos, Bol de la Sociedad Española de Biol, Madrid, 1916.

The following are clinical histories in cases diagnosed as trichocephaline appendicitis. The patients were operated on by me in the Colombia Syndicate Hospital.

CASE 1—C M, a man, aged 22, a laborer, when admitted to the hospital had a temperature of 103 F, respirations, 24, pulse rate, 100. The leukocytes numbered 18,000, neutrophils, 71 per cent, eosinophils, 13 per cent. There was severe recurrent pain in the right iliac region, this began three days before admission and continued with increasing severity. Definite symptoms of peritonitis, marked muscular defense, great sensibility over the abdomen, and a fluctuating mass in the area of the appendix were present. An incision in the abdominal wall opened directly into an abscess, showing fecal contamination and the presence of two macerated helminths, found to be trichocephali. The ova of other parasites were not found on repeated examination of the feces.

CASE 2—M G, a girl, aged 10, entered the hospital with a history similar to that in the preceding case, but without perforation of the appendix. At operation, *Trichocephalus* and *Necator americanus* were found in the appendix.

The cases cited were only two of a large number of cases of appendicitis occurring in the surgical service. Frequently I have operated on patients with classic symptoms of appendicitis and have found appendixes without sufficient pathologic lesions to explain the symptoms. After the two cases cited, the hospital staff adopted the custom of immediately administering an anthelmintic to patients with symptoms suggestive of appendicitis, with the result that there was a marked decrease in the percentage of cases eventually requiring operation.

PERITONITIS

It is natural that localized or general peritonitis might be produced by the perforation of other sites in the large intestine, especially at the hepatic and splenic flexures, sigmoid and rectum, which are points of predilection of *Trichocephalus*. One case in the clinic of the Colombia Syndicate Hospital serves to indicate that this is true.

CASE 3—G O, a man, aged 20, a laborer, entered the hospital with definite symptoms of generalized peritonitis. The leukocytes numbered 21,000, neutrophils, 75 per cent, eosinophils, 15 per cent. Laparotomy was performed. The intestines were markedly congested and the abdomen contained plastic exudate. The intestines were examined carefully throughout without locating any perforation or other source of the infection.

Since we were confused over the possible origin of the peritonitis, the patient was subjected to careful observation. Nothing of interest was found except a marked trichocephaline infection. The patient was given three treatments of oil of chenopodium and convalesced without incident.

In the practice of medicine in the tropics it is common to encounter cases of peritonitis without apparent cause, and to such cases tropical practitioners have given the nickname of "idiopathic peritonitis." No doubt many of these cases are due to infections transmitted through some trauma made in the intestinal wall by intestinal parasites.

Pathologists generally maintain that germs cannot penetrate the intestinal mucous membrane unless there has been a solution of its

continuity by trauma or necrosis. For this reason, among others, different writers have counseled surgeons to manipulate the intestines with gentleness in order to prevent infection through traumatism of the mucosa.

Weinberg⁴ gave food infected with *Bacillus typhosus* to some monkeys. Those infested with intestinal parasites died, those without helminths lived. Studying this matter in epidemics of typhoid in Paris, Guiart and Garin⁴ demonstrated that typhoid was much more frequent in persons with intestinal parasites than in others, and, of the parasites encountered, *Trichocephalus* was considered the most important. Indeed these authors attributed to *Trichocephalus* a decided responsibility as an inoculator of the bacillus of Eberth.

The same relation of *Trichocephalus* to Asiatic cholera was observed in India by Rogers,⁶ while my observations in connection with forty-two cases of bacillary dysentery in Colombia seemed to confirm the relationship.

SEPTICEMIA

Recent Japanese investigators⁷ have demonstrated that the larvae of nearly all intestinal nematodes, even of *Ascaris lumbricoides*, penetrate the intestinal wall and carry out a part of the life cycle in the tissues of the host. It is not difficult to understand that any germ present in the intestinal tract might thus gain access to the blood stream.

During my experience in Colombia there often occurred severe cases of lymphangitis of the legs immediately following penetration of the skin by hookworm larvae ("ground itch"), with occasional instances of infection of the blood stream.

DYSENTERY

In tropical practice I frequently saw cases of a dysentery which presented symptoms typical of amebic dysentery, but without pathologic amebas in the stools. In the majority of these cases the presence of the eggs of *Trichocephalus dispar* was a marked feature.

CASE 4—R. R., a man, aged 22, complained of intense pain in the abdomen, severe tenesmus and frequent bloody stools. Amebas were not found in the feces, but there were numerous ova of *Trichocephalus dispar*. The eosinophilia was 18 per cent. The bacillary dysentery agglutination test was negative. When the patient was treated with emetine his symptoms disappeared slowly, in contrast to the immediate relief it affords in amebic cases. He refused anthelmintic treatment because he had heard that it might be fatal.

In spite of careful diet, hygiene and reduced emetine, his symptoms soon became serious again, and another intensive course of emetine was given him.

Ten days later he returned to the hospital to try the treatment with chenopodium which had been recommended to him. The effect was quick and permanent—with the disappearance of the trichocephali, his dysentery ceased.

6 Castellani and Chalmers. Manual of Tropical Medicine, London, 1920.

7 Nakamura, R. Personal communication to G. Pittaluga, Madrid, 1925.

In thirty-two cases of pure trichocephalic dysentery studied, the symptoms could not be distinguished from those of amebic or bacillary dysentery, but examination of the stool set us right. In each of these cases the patients were immediately relieved by treatment for *Trichocephalus dispar*.

This is a matter of great importance in the tropics where it is the custom to treat with emetine almost every patient who has bloody dysentery. Emetine cures amebic dysentery, but not trichocephalic dysentery. Therefore it is poor practice and unjust to submit a patient suffering with helminthic dysentery to a prolonged and dangerous course of treatment with emetine, under the belief that the patient is merely suffering with chronic amebiasis.

According to my studies, approximately 30 per cent of all cases which clinically appear to be amebic dysentery in the tropics are of trichocephalic origin. These observations were made in the Magdalena River valley of Colombia.

INTOXICATIONS

That the trichocephali are capable of elaborating a toxic secretion which they inject into their host has been shown by Grassi in his excellent study of the pathologic lesions produced by intestinal parasites. In three cases of severe infection caused by *Trichocephalus dispar*, he discovered necrotic areas in the adjacent lymph nodes and degenerations in the nerves and ganglions of the area.

By means of an aqueous extract of the heads and upper third of adult trichocephali, containing the salivary glands, which he injected into rats, he was able to reproduce lesions similar to those mentioned.

For the purpose of ascertaining the origin of the pigment in the intestinal wall of *Trichocephalus dispar*, I performed the following experiment:

Adult trichocephali were washed in physiologic sodium chloride until freed from all earthy material. The worms were ground in a mortar, then extracted successively with boiling alcohol (95 per cent), absolute alcohol and ether. The ether was removed quickly by filtration, and a small quantity of the residue placed on a slide, to which was added two or three drops of Strykowski's solution:

	Gm or cc
Hydriodic acid (without color)	2 drops
Glacial acetic acid	1
Ethyl alcohol (95 per cent)	1
Distilled water	1

The slide was heated almost to the boiling point for twenty seconds, and a solution added by capillarity under the cover-slip. When the slide was examined with a magnification of 400 or more diameters, characteristic black crystals of human hematin hydriodid were seen.

By this modification of the Teichman test it is possible to demonstrate that *Trichocephalus* sucks the blood of its host.

PERNICIOUS ANEMIA

Until the present time no well defined etiology has been accepted as the true cause of pernicious anemia, but the majority of investigators are of the opinion that it has a toxic origin, and various types of intoxication have been associated in its pathology. In the cases reported, a number have been attributed to intestinal parasites, especially *Bothriocephalus latus*. A case associated with *Trichocephalus dispar* was thus described by Lockhart.⁸

A child of 11 years, very anemic, with poor appetite, complained of great debility, diarrhea, abdominal pains, and palpitation, vomiting and vertigo. There were splenomegaly and recurring petechiae beneath the skin.

Hemoglobin, 22 per cent, erythrocytes, 1,200,000, leukocytes, 10,000, eosinophiles, 27 per cent, various megaloblasts and nucleated reds, poikilocytosis, anisocytosis, polychromatophilia. Color index, 1. Wassermann, negative, complement fixation for tuberculosis and Von Pirquet, negative.

The urine and sputum showed no tubercle bacilli. Albuminuria, marked. The feces contained eggs of *Trichocephalus dispar*. All other laboratory and clinical investigations were negative.

Receiving small doses of oil of chenopodium at intervals of ten days for five treatments, the patient expelled 211 male and 306 female trichocephali. The blood picture rapidly improved, and at the end of four months the patient was normal and in very good health.

The primary cause of every case of pernicious anemia is without doubt an individual predisposition, that is, a hematic sensitization of endocrine, hereditary, syphilitic or tuberculous origin. The intoxication by helminths, or other agents, acts secondarily as an excitant to pernicious hemoplasia.

URTICARIA

Azua⁹ included *Trichocephalus dispar* among the parasites which are capable of causing a great variety of dermatologic manifestations, in particular the urticaria group, and described chronic urticarias that yielded to anthelmintic treatment after prolonged and varied therapy for ordinary urticaria had failed.

ACROCYANOSIS DYSTROPHICA

This term refers to various syndromes or symptom groups of hematogenous origin, produced by a variety of intoxications, particularly those of tuberculosis and syphilis, but possibly by intestinal parasites. I studied the following case in the clinic of Prof. Dr. G. Pittaluga, in Madrid.

A. G., a woman, aged 26, unmarried, had had trichocephalus infection for the past eight years. Her family history was uninteresting, her personal history

⁸ Lockhart, R. S. A Case of Pernicious Anemia of Parasitic Origin, West M. Fortnightly, Denver, 1901.

⁹ Azua, J. B. Clinical Lectures in Dermatology, University of Madrid, Session of 1914-1915.

was negative, except for the occurrence of malaria eleven years before. The patient had lived in Costa Rica until the age of 20 where she had contracted the trichocephaliasis, and had been unsuccessfully treated for it.

The erythrocytes numbered 3,900,000, leukocytes, 5,300, eosinophils, 18 per cent. The Wassermann and Sachs-Georgi reactions were negative, the von Pirquet and tuberculous complement fixation tests were negative, the basal metabolism was normal. Tuberculin treatment gave no relief.

Careful clinical examination failed to reveal any disorder, except dermatitis of the hand resembling acrocyanosis, at times accompanied by neuralgic pains.

The patient was given three treatments of oil of chenopodium intramuscularly, she expelled the parasites and the acrocyanosis disappeared and did not return for fourteen months, during which she remained under observation.

PURPURA HEMORRHAGICA

Another case from the clinic of Professor Pittaluga is interesting.

J. M., a woman, aged 21, unmarried, gave a history of prolonged menses, hemorrhages from the gums and spontaneous purpuric foci in the extremities. Nothing in the family or personal history seemed pertinent to her present symptoms.

The Wassermann, Sachs-Georgi and von Pirquet tests were negative, specimens of sputum and urine were negative for tubercle bacilli, roentgen-ray examination was negative. Blood examination showed, erythrocytes, 4,000,000, hemoglobin, 80 per cent, blood platelets, 100,000, leukocytes, 6,200, eosinophils, 14 per cent. The Arneht formula showed a shifting to the left. The stools contained eggs of *Trichocephalus dispar*.

Prolonged treatment with the roentgen rays, calcium salts, thromboplastic serums, endocrine extracts, vaccines and extraction of teeth and tonsilectomy gave only temporary relief. Successful treatment against *Trichocephalus dispar* cured the patient of purpura.

GOITER

R. B., a girl, aged 16, gave a history of thyroid enlargement for five years, which became toxic during the past year. Exceedingly thorough clinical and laboratory examination showed only the presence of a toxic goiter, and *Trichocephalus dispar* infection.

The patient was treated for the trichocephalus infection as a routine measure. In about two months her hyperthyroidism ameliorated. This would have been considered merely as the quiescent phase common in goitrous states had I not happened to read the paper by Borrel¹⁰ dealing with the frequent association of intestinal parasitism with goiter.

As one of the chief functions of the thyroid is to elaborate a detoxifying hormone, it is not unreasonable to believe that it takes part at times in the battle against parasitic intoxication, with resulting hyperfunction.

This case, like the others presented in this paper, has been chosen from a considerable number in each instance, but is not intended to be conclusive. I merely desire to direct attention to the possibility of *Trichocephalus dispar* as an etiologic cause in a great variety of conditions, and to disillusion those who accept it as a harmless parasite.

¹⁰ Borrel, A., Boez, L., and Freyze. Intestinal Parasites in Pathogenesis of Goiter, *Compt. rend. Soc. de biol.* 92:232 (Feb. 6) 1925.

TREATMENT

Oil of chenopodium is the most satisfactory anthelmintic against *Trichocephalus*, as indeed against all nematodes. As *Trichocephalus* tends to lodge in the cecum and appendix, oral medication often fails to reach it. Therefore, in persistent cases it is advisable to inject the chenopodium intramuscularly or intravenously. It is thus eliminated largely through the intestinal tract, and the blood-sucking trichocephali in the appendix get the full benefit.

A brisk purge is always essential two or three hours after anthelmintic treatment, whether by mouth or by injection.

Chenopodium by injection, especially intravenously, is heroic treatment and should be employed only as a last resort in cases in which the patient fails to respond to other measures.

Of course, a fresh, highly-purified oil of chenopodium, from a reliable chemical house, should be employed, and the patient's heart and kidneys should be carefully examined before administration.

I have apparently succeeded in vaccinating dogs against trichocephalus infection by means of a vaccine containing eggs and larvae of *Trichocephalus* which had been carefully ground and inactivated. A report of this work was published in the *Journal of the American Medical Association* ¹¹

CONCLUSIONS

1 *Trichocephalus dispar*, a cosmopolitan intestinal parasite, is of great pathologic importance, and has not been adequately studied.

2 In the Magdalena River valley of Colombia, 92 per cent of 1,336 persons examined had intestinal parasites, of which 41 per cent were *Trichocephalus dispar*.

3 Sixty-two per cent of sixteen autopsies on persons who had died from various causes in Colombia showed *Trichocephalus* infestation, with localization in the cecum, appendix, hepatic and splenic curvatures of the colon, sigmoid and rectum.

4 The subcutaneous injection of eggs of *Trichocephalus despressis-unculus* into puppies produced an infection of the intestinal tract with appearance of ova in the feces.

5 *Trichocephalus dispar* is a definite cause of appendicitis.

6 Many cases of so-called tropical "idiopathic peritonitis" are of helminthic origin.

7 *Trichocephalus* is a factor in the transmission of infections through the intestinal tract, due to its tendency to perforate the intestinal wall, resulting in peritonitis, septicemia, perinephritis and pyelitis.

¹¹ Fernan-Núñez, M. A Contribution to Helminthic Therapy, J. A. M. A. 88 903 (Mar 19) 1927.

8 Approximately 30 per cent of cases commonly diagnosed as amebic dysentery in tropical America are of trichocephalic origin. Anthelmintic treatment is specific in such cases.

9 Purpura hemorrhagica can result from intoxication with the hemolytic enzymes injected in the host by *Trichocephalus*.

10 Acrocyanosis dystrophica, pernicious anemia, urticaria and goiter may be associated with helminthic infestation.

11 The blood pigment in the intestinal mucosa of *Trichocephalus dispar* is human pigment, as can be demonstrated by a modification of the Teichman test.

12 Eosinophilia is commonly more constant and of higher degree in trichocephalic infection than in that produced by other nematodes, indicating that the small number of trichocephali which are usually found are capable of intoxicating the host more than are the usually large number of other helminths.

13 *Trichocephalus* is associated with the hookworm in 33 per cent of all cases (in the tropics). As the hookworm treatment given by mouth is often ineffective against *Trichocephalus*, the campaigns against hookworm are not entirely effectual unless attention is given to the elimination of *Trichocephalus*. If *Trichocephalus* is not eliminated, its symptoms may be attributed to the hookworm. This oversight has been one of the causes why *Trichocephalus* has not received the study which it deserves.

THE QUANTITATIVE DETERMINATION OF BLOOD AMYLASE WITH THE VISCOSIMETER ¹

ROBERT ELMAN, M D

AND

JOHN M McCaUGHAN, M D

ST LOUIS

The presence of a starch splitting ferment in the blood of mammals has long been known and has been the subject of a great many experimental and clinical studies, yet its significance under normal, as well as under pathologic conditions, has remained somewhat of a mystery. This may be due partly to the lack of uniformity and relative inadequacy of the present methods for the quantitative measurement of the enzyme. In connection with other experiments on the external secretion of the pancreas, we became interested in studying blood amylase, and were impressed, as others have been, with certain practical disadvantages of, as well as theoretical objections to, such methods.

METHODS

Two general types of method have been employed in the measurement of blood and urinary amylase. One has been based on the disappearance of the original starch solution, as revealed by its failure to give an iodine reaction, ¹ the other, on the accumulation of sugar as shown by determination of the amount of copper reduction after an arbitrary period of hydrolysis. ² Either method involves certain theoretical objections. A long chain of separate reactions occurs in the diastatic formation of sugar from starch, and the relative activity of the enzyme toward the different parts of the chain remains unknown. The first formation of sugar may occur before all the starch has disappeared, or, conversely, the amylase may hydrolyze all the starch to dextrins before any sugar appears. The selection of one step, therefore, in the measurement of the enzyme activity means that its influence on the other steps is overlooked. Moreover, by these methods the measure of the enzyme has depended necessarily on the amount of change during an arbitrary length of time, since the progress of the reaction has not been followed. As Bayliss ³ points out, "When comparing the action of different strengths of enzyme solutions it is advisable to take as a basis of comparison the times taken

¹ From the Department of Surgery, Washington University School of Medicine and Barnes Hospital.

1 Wohlgemuth, J. *Biochem Ztschr* **9** 1, 1908.

2 Moeckel, K., and Rost, F. *Ztschr f physiol Chem* **67** 433, 1910.

3 Bayliss, W. *The Nature of Enzyme Action*, ed 5, New York, Longmans, Greene & Co., 1924, p 52.

to effect an equal change. This is especially important where the reaction takes place in steps, since only in this manner is it possible to have comparable values."

From the practical point of view, much difficulty is often experienced in selecting an end-point in the iodine reaction for starch, and, in our experience, the same specimen frequently gave widely divergent values. The sugar reduction method has the disadvantage of being relatively more time consuming, and, in the hands of others, as we shall point out, has often led to conflicting results.

By use of the viscosimeter, advantage is taken of the fact that solutions become less viscous as the large molecules dissolved in them are hydrolyzed into smaller and smaller units. In this way, the activity of the enzyme can be studied, regardless of what part of the chain it attacks. By frequent readings, which are quickly and simply made, the change in viscosity can be followed continuously, and a curve can be plotted. In the case of tryptic digestion, Northrop⁴ has reported satisfactory results. Recently, Davison has measured the strength of various diastase preparations in this way,⁵ he has compared this method with the older methods of amylase estimation, and has concluded that it is the most practical and accurate.⁶ In this report we shall be concerned with a more detailed study of its use in the case of blood amylase.

EXPERIMENTAL PROCEDURES

The blood from normal dogs was withdrawn from the jugular vein with a syringe, emptied into glass tubes containing sodium citrate (20 mg to 10 cc of blood), shaken, and centrifugalized to obtain clear plasma. In some cases a part of the blood was allowed to clot, and the clear serum was used. The blood was withdrawn at various stated periods from one to six hours after meals, and, in a few cases, after a fast of from one to three days. The serum or plasma was then added to the starch solution in the viscosimeter in amounts up to 0.8 cc, and readings were made.

Preparation of Starch Solution—A solution of starch was prepared by boiling 7 Gm of soluble starch (Lintner) of the dry powder in 70 cc of distilled water and made up to 100 cc with fifteenth molar phosphate buffer of p_H 6.7. In a cotton stoppered flask, the solution was autoclaved for half an hour, it was then filtered, and the crystal clear solution used at once. It was necessary to make a fresh solution each time, for, on standing, a precipitate formed.

Viscosity Readings—Five cubic centimeter portions of the starch solution were placed in each of several Ostwald viscosimeters of a suitable size and of a bore that permitted water to pass from the upper to the lower mark during about twenty seconds. In such a tube, the solution of starch, prepared as already mentioned, took from forty to forty-five seconds to pass the same distance. The tubes were immersed in a water bath (with glass walls to permit observation) maintained with a thermostat at a constant temperature of $37.58^\circ C \pm 0.1$.

The period of outflow was determined by a stop watch, the solution first being drawn just past the upper mark. Several control determinations

4 Northrop, J. H., and Hussey, R. G. *J. General Physiol.* **4**: 353, 1922.

5 Davison, W. C. *Bull. Johns Hopkins Hosp.* **37**: 281, 1925.

6 Maslow, H. L., and Davison, W. C. *J. Biol. Chem.* **68**: 75, 1926.

were made over a period of several minutes before the plasma to be tested was added. The outflow time was measured to 0.2 of a second. Readings were made at first as rapidly as possible, but as the reaction proceeded, only after every ten or fifteen minutes. The time in seconds of the initial reading was taken as 100 per cent and all subsequent readings after the addition of the plasma as percentages thereof.

EXPERIMENTAL OBSERVATIONS

The observations in the case of a specimen of normal serum is represented in the accompanying graph (chart 1). The curve is apparently a logarithmic one, but calculation of K for the monomolecular equation did not yield constant values, though they tended to become constant as the reaction proceeded.

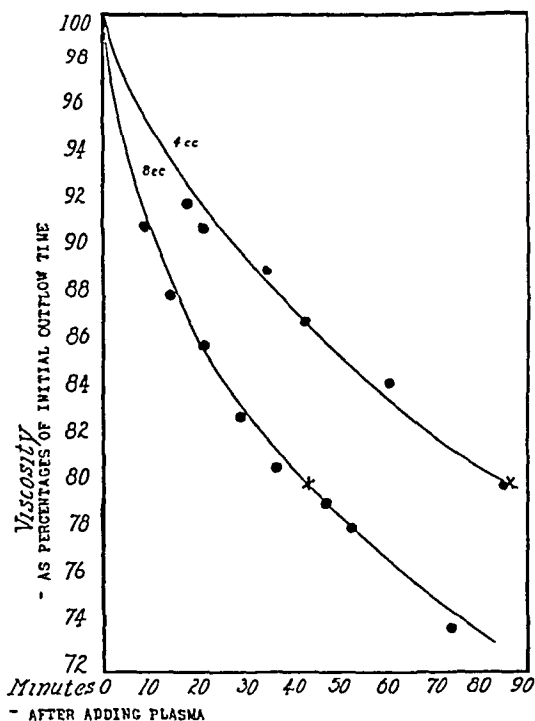


Chart 1—Graph plotted from determinations of the viscosity of the starch solution after the addition of plasma from a normal dog.

From the practical point of view, however, it was at once apparent that a simple linear relationship existed between the amount of enzyme and the length of time required to effect a given change (20 per cent) in the time of flow, that is, in the viscosity. In the instance mentioned, for example, with 0.4 cc of plasma, the outflow time was reduced from forty-six seconds to thirty-seven seconds in eighty-five minutes, and with 0.8 cc from forty-six to thirty-seven seconds in forty-three minutes. The same inverse ratio was found in repeated trials on the same blood, as well as on blood from fifteen different dogs. To test the relationship still further, a specimen of blood possessing an increased amylolytic power was tried. This was obtained from a dog in which pancreatic obstruction

had occurred, and showed within a greater range the same observations represented in chart 2. Here it will be noted that the time required to cause 20 per cent reduction in outflow time for various amounts is as follows: for 0.05 cc, eighty-six minutes, for 0.1 cc, forty-two minutes, for 0.2 cc, twenty-two minutes, and for 0.4 cc, eleven minutes.

Formulation of Arbitrary Units—To avoid expressing the amount or concentration of enzyme in units of time, it seemed convenient to translate these values into another form. An arbitrary change of 20 per cent in the outflow time was selected and one amylase unit defined as the amount of enzyme which would accomplish this change of vis-

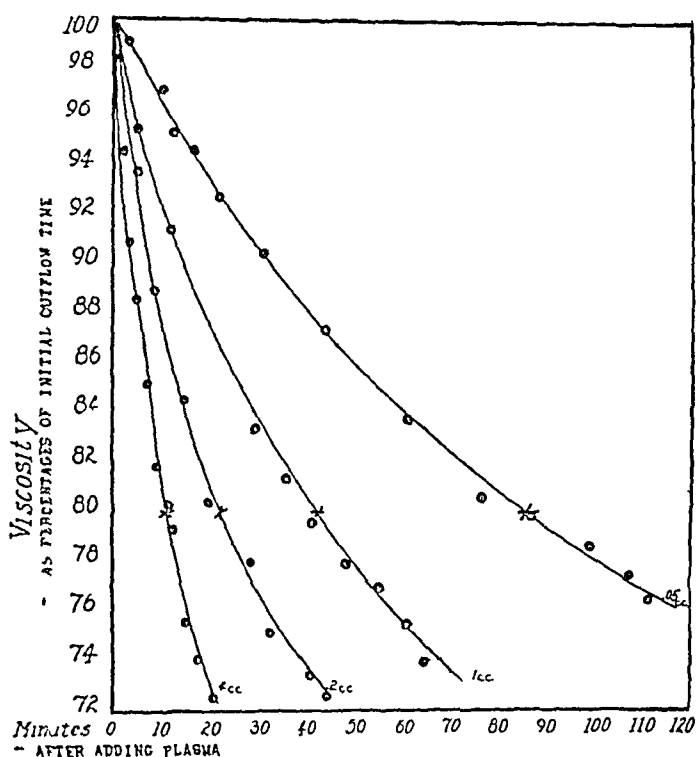


Chart 2—Graph plotted from determinations of the viscosity of the starch solution after the addition of plasma from a dog in which pancreatic obstruction had occurred

cosity in one hour—the same term used by Northrop⁴ in defining the trypsin unit. The relationship between time of change and quantity of amylase, as indicated by the results cited in the foregoing, follows Arrhenius' rule, $Q = \frac{1}{T}$, and by definition, $U = \frac{60 \text{ (minutes)}}{T \text{ (in minutes)}}$. To introduce concentration of enzyme, the factor of volume is added, giving as the final formula

$$U = \frac{60}{TV}$$

in which U is amylase units per cubic centimeter, T is minutes required to reduce the outflow time of the starch solution 20 per cent, V is the volume in cubic centimeters of the enzyme sample required to effect this change

Uniformity of the Amylase Content of Normal Blood—The amylase units contained in normal blood were relatively uniform. In all but one of thirteen dogs, 0.4 cc of plasma reduced the outflow time 20 per cent in from sixty to one hundred minutes, or, using the aforementioned formula, the values were between 2.5 and 1.5 units (table 1). In cases of pancreatic obstruction, as will be reported in a succeeding paper, this value may rise to as high as 75 units within twenty-four hours. In the instance represented in chart 2, it was 15 units.

The influence of food, as is indicated in table 1, was almost negligible. Whether the animal had fasted for a day or had eaten within an hour, there was little deviation from the normal.

Units of Amylase in the Blood of Dogs

Dog	Sex	Weight in kg	Hours Since Feeding	Amylase Units
1	M	10	6	1.7
2	F	12	6	1.4
		1 week later	72	2.1
		3 weeks later	6	1.8
3	M	11	6	2.0
4	M	18	5	2.2
5	F	12	6	1.7
6	M	10	3	2.0
7	F	10	3	2.2
8	F	10	3	1.8
9	M	14	3	6.7
10	M	12	7	2.5
11	M	12	54	2.0
		1 week later	14	2.5
12	F	11	21	1.6
		3 days later	14	1.8
13	M	14	4	1.8

Comparisons between plasma and serum were made in a number of instances, and no difference was detected between the two, provided the examinations were made within an hour or two after the blood had been withdrawn. This indicates the absence of any immediate effect from citrate. If the blood was allowed to stand, however, even in the icebox, marked deviations were found. The plasma uniformly deteriorated, losing 50 per cent or more of its amylolytic power within a day or two. The serum, for some unknown reason, retained its potency and actually became stronger in several instances.

Amylase in the Blood of Dogs in Which the Total Pancreatic Juice Had Been Drained—In three dogs in which intubation for the collection of the total external secretion of the pancreas was performed, examination of the blood revealed the following value for the blood amylase: 1.8, 1.5 and 2 units.

Drainage of the total pancreatic juice under sterile conditions was performed by a method described elsewhere.⁷

⁷ Elman, R., and McCaughan, J. M. *J. Exper. Med.* 45: 561, 1927.

COMMENT

Despite the many observations on the amylase content of human blood and of the blood of the dog, it is difficult to determine any degree of uniformity among them, mostly, perhaps, because of the many differences in the method used. In general, there seems to be some agreement that blood amylase is more or less constant in the normal organism. Wohlgemuth,¹ however, found great variations in the human blood from more than eighty cases, and Cohen⁸ found the value in dogs ranging between 13 and 67. Markowitz and Hough⁹ reported variations between 9 and 25 in fifteen normal dogs. In the study of human disease, using the same method, Meyer and Killian¹⁰ found definite variations, whereas Lewis and Mason¹¹ were unable to confirm them.

The method herein described does not have the theoretical objections already mentioned. It has proved simple and easy to carry out, and the readings are entirely objective. The accuracy on repeated determinations of the same specimen has been within 5 per cent. Specimens of blood from normal canines have yielded values varying between 1.5 and 2.5 units in a series of thirteen animals. No change was observed after a fast, and it could not be detected that meals had any influence.

Several possible sources of error should be mentioned. The zero point, that is, the initial viscosity, might be altered by the mere addition of serum, quite apart from its amylolytic action. The first few values however, as is shown by the charts, always fell fairly close to the curve. The viscosity of serum, it was found, is about the same as that of the starch solution we were using, so that there was no alteration of the initial viscosity in this way. In the case of urine, this was not true, and as will be pointed out in a succeeding paper, a correction for the zero point was necessary in determining the concentration of certain specimens of urine containing amylase.

The influence of moderate differences in the initial viscosity of the starch solution prepared at different times was considered. It was inconvenient to adjust each solution to the same viscosity, but, in testing the same serum with starch solutions of various viscosities (between that expressed by a time outflow of forty and forty-six seconds), the calculated activity differed not more than 5 per cent.

The significance of the blood amylase in dogs in which the total pancreatic juice had been drained may be surmised from the three experiments here reported, in which no reduction in the blood amylase occurred following several days of drainage of the total pancreatic juice. From this it may be inferred that if the blood amylase is of pancreatic origin,

8 Cohen, S. J. *Am J Physiol* **69** 125, 1924.

9 Markowitz, J., and Hough, H. B. *Am J Physiol* **75** 571, 1926.

10 Meyer, V. P., and Killian, J. A. *J Biol Chem* **29** 179, 1917.

11 Lewis, D. S., and Mason, E. H. *J Biol Chem* **44** 455, 1920.

the intestinal absorption of diastase plays little or no part in the maintaining of the level of the enzyme in the blood. On the other hand, if the ferment is resorbed from the ducts, the leading off of the pancreatic juice to the outside does not prevent its occurrence.

SUMMARY

A method is described for the quantitative estimation of amylase based on the time required to effect an arbitrary reduction in the outflow time in a viscosimeter of a buffered starch solution. The time values thus obtained were found to vary in simple inverse relation with the concentration of amylase. An arbitrary amylase unit was selected as representing the concentration of enzyme capable of lowering the viscosity of 7 per cent starch solution by 20 per cent in one hour. Using this standard, we found that the amylase content of the plasma of normal dogs fell between 1.5 and 2.5 units. Fasting did not alter this range, and meals did not have any influence. In three instances in which the total pancreatic juice was draining to the outside, the amylase content of the plasma was within these same limits.

The method has proved simple and easy to carry out, and would seem to be readily adopted for routine use.

TUBERCULOSIS FOLLOWING DELIVERY ORIGINATING FROM GENITAL TUBERCULOSIS

ACUTE MILIARY FORM

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AND

H WALDEN RETAN, M D

SYRACUSE, N Y

Acute miliary tuberculosis has been so thoroughly studied that the mere citation of an additional case would not be of particular interest. It is well known that the disease usually originates from tuberculosis of the intima of a blood or lymph vessel, sometimes by the penetration of a caseous focus into a vessel wall. A rupture of the caseous area suddenly throws millions of tubercle bacilli into the blood stream, these are sifted out by various organs and lead to the formation of innumerable miliary tubercles. A survey of the literature shows few reported cases in which the disease has originated in the female generative organs and has been definitely influenced by pregnancy or delivery.

REPORT OF A CASE

History—Mrs V, aged 20, married seventeen months, five months pregnant, was admitted to the Syracuse Memorial Hospital on Dec 29, 1924. A grandfather had died of tuberculosis, otherwise the family history was not important. The patient gave a past history of measles, pertussis and scarlet fever, with full recovery from all. She had had no operations or accidents, she did not take cold easily and had never been seriously ill. Menstruation began at 13 and was always regular, with dysmenorrhea and scanty flow. She had had one previous miscarriage brought on by herself a year before her admission to the hospital. Her last menstruation occurred five months before admission. She denied any interference with this pregnancy. One week previously she had had an acute cold and cough, but was not seriously incommoded, and was able to do her work about the house. Thirty-six hours before admission she noticed a slight vaginal discharge which became bloody the following day, accompanied by violent colicky abdominal pain. A few hours after entrance to the hospital, she expelled a five months' fetus. During the next five days the lochia became foul and profuse, and the patient coughed considerably, but the result of frequent examinations of the chest were negative. At the end of a week the lochia diminished in amount, the odor disappeared and the cough lessened. However, in spite of an apparently good general condition, the temperature rose to 103.6 F the day after the miscarriage, and the pulse rate to 125. For more than three months the patient continued to have a septic type of temperature, averaging 102 or 103 F in the evening, with a daily variation of from 2 to 4 degrees between the low and high points. The pulse was constantly rapid, and the respirations averaged from 18 to 22. After seeing the patient laugh and joke with other patients, and noting her good general condition, it was difficult to believe that she was suffering from a serious illness.

Examination—The patient was a slender young woman with bright eyes and a somewhat delicate appearance. Ophthalmic examination showed a persistent hyaloid artery. Results of examinations of the chest were at first negative, but

on March 17, 1925, a few transient fine râles were heard at the left base in the posterior axillary line. After this date occasional scattered râles were heard, but no definite pathologic signs could be distinguished. Shortly after entrance to the hospital, an elongated mass—firm and slightly tender—was noted in the right lower abdominal quadrant. Examination of the vagina disclosed a sub-involuted uterus with a thickening in the region of the right broad ligament. This area on the right gradually increased to the size of an orange, was apparently in front of the broad ligament, not tender and probably separate from the mass in the right lower quadrant.

On Jan 21, 1925, a roentgenogram of the chest showed rather dense shadows in the hilum. The markings of the lung were rather prominent, with considerable stippling throughout both sides. The observation was considered suggestive of peribronchial and glandular reaction.

On March 7, a roentgenogram of the chest showed a marked increase in the stippling and mottling throughout the parenchyma of the lung. The distribution was uniform from the apices to the bases. The appearance suggested a possible miliary tuberculosis.

On April 7, no change was noted in the roentgenogram of the chest.

On February 14, following a barium meal and barium enema, it was reported that the region of the cecum failed to fill in the usual manner, and that the observations were rather suggestive of some abnormality in this region. The roentgen-ray department deserves credit for being the first to diagnose miliary tuberculosis in this patient.

Repeated blood cultures and the blood Wassermann reaction were negative. Numerous blood counts gave the following averages: red blood cells, 3,000,000 plus, hemoglobin, from 70 to 75 per cent, leukocytes, from 6,000 to 8,000, and neutrophils from 66 to 80 per cent. The differential count was normal. Toward the latter part of her illness the leukocyte count tended to rise moderately.

The urine showed the constant presence of a faint trace of albumin and a moderate number of leukocytes—also found in catheterized specimens. Numerous examinations of the sputum were negative for tubercle bacilli.

Course of Illness and Operation—Despite the continued septic temperature, the patient's condition remained fairly good, she coughed little and was out on the roof when the weather permitted. The report of the roentgen-ray department on March 7 of possible miliary tuberculosis did not meet with general acceptance in view of the other observations. An increase in the size of the pelvic mass led to a decision to operate.

On March 26, a midline incision was made from umbilicus to symphysis. When the peritoneal cavity was opened, an inflamed mass was found in the right side of the pelvis in the region of the broad ligament. Several loops of ileum with the omentum were firmly adherent to each other. On separating these the exploring finger entered an abscess cavity in the region of the right broad ligament. This contained about 30 cc of thick, yellow pus with the odor of *Bacillus coli*. Only a little of the parietal peritoneum could be seen. At several points, however, on both parietal and visceral peritoneum were small tubercles—1 or 2 mm in diameter. The wound was closed with silkworm gut sutures and a cigaret drain.

The patient made a satisfactory postoperative recovery, but the temperature continued to run the same septic course, entirely unaffected by the operation. The incision failed to heal and soon broke down. A profuse yellow discharge with fecal odor came from the wound, the edges of which began to gape. The patient commenced to decline rapidly. The pulse grew weaker, and on April 4 she became irrational and would not eat. On the 6th she could not see, and on the 8th she went into a stupor. On April 9th the head and eyes were turned to the left and the left pupil was larger, lateral, and at times vertical, nystagmus were noted. Marked internal strabismus was present on the right. Froth issued from the right side of the mouth. The neck was not rigid. The lungs were clear and the breathing was quiet. Knee jerks were absent. There were no abnormal reflexes.

Examination of the fundus showed no change Lumbar puncture on April 10 gave a negative fluid, with no tubercle bacilli demonstrable The patient died on April 11

Autopsy—(Performed by Dr T C Wyatt, assisted by Dr C C Carpenter) The body was that of a fairly well developed and poorly nourished woman, estimated length, 155 cm, estimated weight, 100 pounds Rigor mortis was moderate Livor mortis was moderate in the dependent parts The scalp, ears and nose were normal The pupils were moderately constricted and equal There was a brownish discoloration of the lower portion of the left conjunctiva The mouth was foul Several teeth were missing, those remaining were in fair condition Superficial lymph nodes were not palpable In the lower portion of the abdomen, in the midline between the umbilicus and pubis, there was a longitudinal incision about 9 cm in length, the walls of which were reddish and covered with grayish purulent material The lower portion of the incision was open and was about 4 cm wide, being packed with gauze When the gauze was removed there was an opening into the peritoneal cavity, and a moderate amount of grayish purulent material was seen just above the symphysis pubis This wall was apparently not healing The upper and lower extremities were normal

The peritoneal cavity contained no free fluid Scattered over the visceral and parietal peritoneum were elevated grayish areas, the average size of which was about that of a pinhead These were also scattered along the intestines and mesentery There were fibrinous adhesions between the liver and the diaphragm and between the spleen and the diaphragm The diaphragm extended to the third rib on the right and to the fourth rib on the left The foramen of Winslow was open The lesser peritoneal cavity was normal The mesenteric lymph nodes were not enlarged The appendix was free and without evident lesion The right tube extended up to the lower portion of the cecum and was adherent to it About 1 cm above the base of the appendix was an irregular, rounded perforation into the cecum about 0.5 cm in diameter About 2 cm above this and in line with it, on the anterior surface of the cecum, was a similar perforation about 2 cm in diameter The walls of each of these were smooth and apparently not thickened The coils of the small intestine were matted together by fibrinous adhesions The remainder of the large and small intestines was without evident lesion as examined, with the exception of those already described The uterus was retroverted and appeared dark red, between it and the bladder was a fairly large amount of grayish purulent material

The pleural cavities contained no free fluid Scattered over both visceral and parietal pleurae were irregular, rounded, grayish, pinhead-sized, elevated areas There were no adhesions around the lungs

The pericardial cavity contained from 15 to 20 cc of slightly cloudy amber fluid Beneath the epicardium were reddish, pinhead-sized punctate areas of hemorrhage The pulmonary artery opened in situ revealed no embolus Over the parietal pericardium in the region of the right auricle was a grayish, slightly thickened area about 1 cm in diameter Otherwise the pericardial cavity was without evident lesion

The weight of the heart was 175 Gm The epicardium was without evident lesion, with the exception of that described in the foregoing On section, the valves were without evident lesion Beneath the endocardium, more marked in the left ventricle, were irregular dark reddish areas of apparent hemorrhage The myocardium was brown In the region of the left ventricle there were apparently three or four grayish, pinhead-sized areas in the substance of the myocardium

The weight of the right lung was 350 Gm, that of the left was 340 Gm The bronchi and pulmonary vessels were without evident lesion The lungs were crepitant throughout On section, irregular, rounded, grayish areas varying in size from that of a pinhead to 3 mm in diameter were seen scattered over the cut surface in a fairly uniform distribution In the upper right lobe there was a rounded area about 2 cm in diameter, the center of which contained a grayish,

moderately dry, "cheesy" material. Around the "cheesy" material the lung tissue was dark red. The wall of this did not appear unusually thickened. A moderate amount of grayish, frothy material could be expressed from the cut surface.

The weight of the spleen was 125 Gm. Scattered over the outer surface of the spleen were elevated, grayish, pinhead-sized areas. On section, a few similar grayish areas were seen on the cut surface. The markings were fairly distinct.

The weight of the liver was 1,125 Gm. Scattered over the surface of the liver were grayish, elevated areas from 1 to 4 mm in diameter. On section, the cut surface of the largest of these areas appeared somewhat "cheesy." Three or four pinhead-sized, grayish areas were seen on the cut surface.

The gallbladder and ducts were without evident lesion.

The weight of the kidneys was 225 Gm. They were not unusual in their external appearance. On section, the markings were distinct. Scattered over the cut surface were a few pinhead-sized, grayish areas. The capsule stripped easily, leaving a smooth surface.

The suprarenals were without any evident lesion.

In the lower end of the ileum near the ileocecal junction there were a few irregular superficial yellowish ulcerations varying in diameter from 2 to 10 mm. On one side of the larger perforation in the cecum, described in the foregoing, there was a similar irregular area of superficial ulceration about 8 mm in diameter. With the exception of this area, the inner margins of the perforation showed no evidence of change.

The pancreas was without any evident lesion as examined.

On the peritoneal surface of the pelvic organs were numerous pinhead-sized, grayish, elevated areas similar to those found in other portions of the peritoneal cavity. In the inner third of the right fallopian tube there was an irregular perforation, the tissues around which tended to be dark red. There were areas both in the wall of the tube adjacent to the perforated portion and in the adjoining tissues which were yellowish and somewhat "cheesy." The outer two thirds of this tube contained a quantity of yellowish "cheesy" material, and the mucous membrane in this region was roughened and irregular. The lumen of the left fallopian tube in the distal two-thirds contained a small amount of yellowish "cheesy" material. At the junction of the left fallopian tube and the horn of the uterus there was a collection of yellowish "cheesy" material from 1 to 1.5 cm in diameter. The endometrium of the entire uterus was roughened and irregular, and presented numerous irregular, yellowish areas varying in diameter from that of a pinhead to from 3 to 4 mm, which were apparently numerous small, irregular, superficial ulcerations. Except that it seemed slightly roughened, the cervix was without evident lesion.

The aorta showed a few slightly elevated irregular yellowish areas.

The weight of the brain was 1,275 Gm. It filled the dura without evidence of distention. Convulsions were visible through the dura. At the base of the brain and extending out for a short distance into both sylvian fissures, there was a small quantity of yellowish-gray exudate in the pia-arachnoid. Scattered along the vessels at the base of the brain, fairly numerous pinhead-sized, grayish elevations could be distinguished in the pia-arachnoid. On section, the ventricles contained slightly more fluid than usual, and it was slightly cloudy. Just outside and beneath the middle portions of the floor of each lateral ventricle there was a rounded, yellowish area from 3 to 4 mm in diameter, the extreme periphery of which seemed slightly darker than the surrounding brain tissue. The brain, on section, was otherwise without evident lesion.

The base of the skull was without evident lesion.

The middle ears were without evident lesion.

The anatomic diagnosis was tuberculous endometritis, bilateral tuberculous salpingitis, pelvic abscess on the right side, tuberculous peritonitis, miliary tuberculosis of the lungs, miliary tuberculosis of the kidneys, tuberculous meningitis, tubercles in the substance of the brain, probably tuberculous ulcerations in the ileum and cecum and slight arteriosclerosis.

Microscopic Examination—The heart showed a slight fatty degeneration, tending to be just beneath the endocardium

There were miliary and conglomerate tubercles in the lungs. Slight edema was present. Sections from the wall of the small cavity (see gross description) showed a few tubercles, exudate and hemorrhage—apparently a relatively recent process with little evidence of connective proliferation.

Tuberculosis with hyalinization of the connective tissue was found in the bronchial lymph node.

Evidence of miliary tuberculosis was found in the spleen.

There was miliary tuberculosis of the liver. A slight fatty change tended to involve the central portions of the lobules.

On the kidneys were miliary and conglomerate tubercles.

The brain showed tuberculous meningitis. Small "solitary" tubercles occurred in its substance.

Examination of the uterus revealed tuberculous endometritis and myometritis.

There was tuberculous salpingitis in the fallopian tubes.

The cecum showed tuberculosis with perforation.

Comment—As a result of the study of the gross material and microscopic sections, it seemed probable that the genital tuberculosis was the source of the general miliary tuberculosis as well as of the tuberculous peritonitis and the tuberculosis of the cecum. The tuberculosis of the uterus was apparently a relatively old process, probably causing the abortion in December, following the abortion, it probably progressed rather rapidly and, with secondary infection, resulted in pelvic abscess and later in general miliary tuberculosis. The relationship of the tuberculosis of the cecum to the pelvic tuberculosis and peritoneal tuberculosis is indefinite. However, the involvement of the cecum was apparently rapidly progressive with little evidence of connective tissue proliferation, and might have occurred within a relatively short time. The finding of what was apparently a relatively old tuberculous infection of the bronchial lymph node with hyalinization suggests the possibility that the genital tuberculosis was secondary to an obscure focus in some other portion of the body rather than being itself primary.

REVIEW OF THE LITERATURE

In 1897, Claribel Cone¹ reported in great detail a case of encysted dropsy of the peritoneum secondary to uterotubal tuberculosis and associated with tuberculous pleurisy, generalized tuberculosis, miliary tuberculosis of most of the organs, and pyococcal infection. She concluded that the disease began as a low grade tuberculous inflammation of the pelvic viscera some time before pregnancy, and that the phenomena incident to pregnancy and the puerperium excited the process to increased activity. General infection of the blood stream later ensued. Usually, tuberculosis of the tubes and peritoneum is secondary to tuberculous disease elsewhere, most commonly in the lungs, but in her case no old foci were found. She believes that primary tuberculosis of the tubes may originate by infection through the blood stream or from without through the vagina. The latter route appears more probable.

Newman² gives a brief report of the case of an Indian woman, aged 36, who apparently developed puerperal infection a few days after childbirth. She had high fever, rapid pulse and respiration, evidence of dis-

1 Cone, Claribel. Bull. Johns Hopkins Hosp. 8: 91, 1897.

2 Newman. J. Oklahoma M. A. 12: 347, 1919.

ease in the right lung (pneumonia?), tenderness of the right ovary, swelling and tenderness of the uterus and phlegmasia alba dolens. There were 15,000 leukocytes. The patient died four weeks after childbirth. Newman stated that the autopsy showed acute miliary tuberculosis, but he gave no further details.

Robinson³ reported the case of a woman, aged 22, who died at the Presbyterian Hospital, Chicago, two months after delivery at term. Autopsy showed focal tuberculosis of the right tube with acute miliary tuberculosis.

Audion⁴ reported the case of a girl, aged 13, not pregnant, who died after an illness of three and a half weeks. Autopsy showed acute miliary tuberculosis and caseous tuberculosis of the uterus and tubes.

Kraus⁵ reports two cases, the first being of a somewhat different type. A woman, aged 23, four months pregnant, was admitted to the hospital with manifest pulmonary tuberculosis and a sputum positive for tubercle bacilli. She died four weeks later, undelivered, with signs of acute miliary tuberculosis of the lungs. Autopsy confirmed these observations and also disclosed chronic tuberculosis in various organs. The uterus, placenta and tubes showed well marked tuberculous changes. The second patient was a woman, aged 31, five months pregnant, who was admitted to the hospital with a diagnosis of pulmonary tuberculosis. She aborted in three days and died three weeks later. Miliary tuberculosis of many organs was found, with chronic lesions in the lungs and uterus. The tubes were free from disease. He quotes similar cases reported by Lehman,⁶ Schmorl and Kokel,⁷ Rokitsansky,⁸ Breus,⁹ Stolper,¹⁰ Davidsohn,¹¹ and Hunermann.¹²

Kraus states that it is a well known fact that a latent or obsolete tuberculosis of the respiratory organs often develops into acute miliary tuberculosis in childbed. Other cases may show generalization from a tubal tuberculosis which later spreads to the uterus. In a third type, as reported by Hunermann, infection in the blood stream developed from infection of the placenta which in turn followed tubal tuberculosis (Westenhofei).¹³

In 1917, Gertiude Cuny¹⁴ reported a case of her own and was able to collect eight additional cases, two of which had been mentioned by

3 Robinson N Am Pract **19** 1897

4 Audion Gaz hebdomadaire de med **3** 217 (March) 1898

5 Kraus Ztschr f Geburtsh u Gynak **52** 437, 1904

6 Lehman Deutsche med Wchnschr 1893, p 200

7 Schmorl and Kokel Beitr z path Anat u z allg Pathol **16** 313

8 Rokitsansky Allg Wien med Ztg, 1860, vol 21

9 Breus Wien med Wchnschr, 1877, vol 44

10 Stolper Stolper's Monatsschr f Geburtsh u Gynak **11** 354

11 Davidsohn Berl klin Wchnschr 1899, p 547

12 Hunermann Arch f Gynak **43** 40

13 Westenhofei Deutsche med Wchnschr, 1903, p 221

14 Cuny, G Thesis, Berlin, 1917

Klaus¹⁵ A woman, aged 28, had a slight rise of temperature following delivery, but felt well enough to leave the hospital in one week. Eight weeks later, she was readmitted with symptoms of sepsis and severe psychic disturbances. She died the next day. Autopsy revealed general military tuberculosis, severe tuberculosis of the uterus, a chalky tuberculous gland the size of a walnut just above the bifurcation of the trachea and a smaller calcified gland at the right hilum. The right tube was completely transformed into a necrotic mass containing a few tubercle bacilli, and the mucous membrane of the fundus of the uterus was similarly involved. The process in the thoracic lymph glands was old. Probably the infection occurred in childhood, as the patient's mother had died of tuberculosis.

The eight additional cases with autopsy observations reported by Cuny showed similar characteristics. Three patients went to full term and five aborted. In addition to general military tuberculosis, all of the patients showed caseous tuberculosis of the internal generative organs. Usually the uterus and one or both tubes were involved. In three cases old tuberculous foci were present in the lungs and peribronchial lymph nodes. In three cases no old tuberculous disease could be found outside of the pelvic organs. In one case there was no focus in the thorax, but peritoneal tuberculosis was present. In the eighth case (Weichselbaum¹⁶) the condition of the other organs was not made clear, but the microscopic observations are of particular interest. At the site of the insertion of the placenta (abortion at four months), there were several caseous nodules, some of which extended to the walls of the thrombosed veins and seemed to be connected with the thrombi inside the latter. The tuberculosis had evidently developed first in the tissue and had extended to the veins, the walls of which it had penetrated. As some of the tubercles in the veins were caseated, they were evidently the starting point of the general military tuberculosis. In all of the eight cases, except that of Schellong,¹⁷ the uterus was seriously involved and was evidently the starting point of the military tuberculosis, in his case only one tube was involved, the uterus being free. Cuny believes that uterine tuberculosis may cause abortion. Cuny's eight collected cases include two by Weil¹⁸ and one each by Westenhofer¹³ and Frankenburger¹⁹.

COMMENT

Acute military tuberculosis following delivery is undoubtedly more common than is generally realized. The fact that medical literature in English is almost lacking in case reports, and that a definite though

15 Davidsohn (footnote 11) Hunermann (footnote 12)

16 Weichselbaum *Munchen med Wchnschr* 1884, nos 12 and 13

17 Schellong *Centralbl f Gynak* 1885, vol 27

18 Weil *Medical Dissertation*, Strassburg, 1909

19 Frankenburger *Munchen med Wchnschr* 1884, nos 12 and 13

small number has been collected from continental sources probably depends on the relative difference in the frequency of autopsies. The diagnosis is seldom made during life. Most of the unrecognized cases are undoubtedly classed as puerperal sepsis. Genital tuberculosis may arise primarily by infection from without through the vagina, or may be secondary to a focus elsewhere in the body, notably in the respiratory organs. The strain incident to pregnancy or delivery may cause increased activity of the disease with general dissemination by way of the blood stream, leading to miliary tuberculosis of various organs.

CONCLUSIONS

- 1 When women continue to have fever and repeated negative blood cultures after delivery, acute miliary tuberculosis should be considered.
- 2 Routine roentgenograms of the chest may be of great diagnostic aid.

THE EFFECT OF THYROID MEDICATION IN NEPHROSIS *

SHIH-HAO LIU, M D

PEKING, CHINA

With the recent advances in the study of blood chemistry and metabolism, there has been gathered more and more evidence in support of the view that the nephritis often called chronic parenchymatous nephritis results from some general metabolic disorder Epstein¹ is one of the foremost exponents of this theory. He calls this type of nephritis nephrosis, regarding it as fundamentally different from all the other types. It is characterized by insidious onset, apparently unassociated with any known infection, by anasarca and effusion into the serous membranes, by marked albuminuria, with or without casts, by changes in the blood chemistry, namely, reduction of plasma protein, inversion of albumin-globulin ratio and increase of blood lipoids (cholesterol), and, finally, by a decrease of basal metabolism. In contrast to other kinds of nephritis, there is, at least in the early stages, no hypertension, cardiac enlargement, hematuria or marked retention of nonprotein nitrogen in the blood.

The most characteristic changes are low plasma protein and hypercholesterolemia. With the decrease of plasma protein, the osmotic pressure due to the colloids of the blood, which counteracts the intracapillary pressure, is diminished, thus allowing a free transudation of blood fluids from the capillaries to the tissues and enhancing the ability of the tissues to hold water and salts. This constitutes the mode of production of edema in nephrosis, according to the hypothesis of Epstein. The fact that in complete nephrectomy, in tubular nephritis, in mercury poisoning and in chronic interstitial nephritis there may be anuria or extreme renal insufficiency without the appearance of edema, indicates that edema does not depend entirely on the changes in the kidney and adds much weight to the theory. The increase of blood lipid with the decrease of basal metabolism² suggests that there are changes that affect the bodily mechanism as a whole, the kidney disturbances being a part of the whole picture.

Kaufmann,³ in a clinical and pathologic study of nephrosis, also comes to the conclusion that edema has little relation to the kidney, but

* From the Department of Medicine, Peking Union Medical College. Presented before the China Medical Association Conference, September, 1926.

1 Epstein, A. A. *Am J M Sc* **154** 638, 1917, **163** 167, 1922, *M Clin N Amer* **4** 145, 1920, **5** 1067, 1922.

2 Epstein, A. A., and Lande, H. *M Rec* **100** 1096, 1921.

3 Kaufmann, J., and Manson, E. Nephrosis, Clinical and Pathologic Study, *Arch Int Med* **35** 561 (May) 1925.

depends on altered capillary permeability as a result of a general systemic cellular degenerative process of unknown origin. Clausen⁴ also regards parenchymatous nephritis in children, which corresponds to Epstein's nephrosis, as a general systemic disorder. The serum surface tension in such cases⁵ is much diminished, thereby increasing the permeability of colloidal membranes to protein, with resultant edema.

As to the etiology, while Clausen⁶ was able to demonstrate the presence of a paranasal infection in his series of eleven cases of nephrosis, a precedent infection was not found in the cases reported by other authors.⁷ On the other hand, the increase of blood lipid with a decrease in basal metabolic rate, and the demonstration of myxedema or the less manifest hypothyroid states in a certain proportion of cases of nephrosis⁸ would speak for thyroid deficiency. With this view in mind, observations on the effect of thyroid extract on nephrosis are interesting.

As early as 1912, Percy⁹ used thyroid extract in thirty-five cases of nephritis of all types, with good results, and later¹⁰ recommended its use in patients with nephritis on whom operations are contemplated. Phipps¹¹ reported seven cases of nephritis, in which the patients were benefited by the thyroid treatment. Bowen and Boothby¹² reported that in two cases of myxedema associated with chronic nephritis and edema, thyroid medication was followed by improvement in the renal condition as well as in the hypothyroidism. In three other cases unassociated with myxedema, the patients were not affected by the administration of thyroid extract. The reports of these cases, however, are not detailed enough to allow definite conclusions.

Eppinger,¹³ impressed by diuretic effect and apparent curative properties of thyroid extract in certain forms of edema, undertook a study of the mechanism of its action. He found that in normal

4 Clausen, S. W. Parenchymatous Nephritis, As General Systemic Disorder, *Am J Dis Child* **29** 581 (May) 1925.

5 Clausen, S. W. Parenchymatous Nephritis, Surface Tension of Blood Serum, *Am J Dis Child* **29** 594 (May) 1925.

6 Clausen, S. W. Parenchymatous Nephritis, Infection of Paranasal Sinuses as Etiology, *Am J Dis Child* **29** 587 (May) 1925.

7 O'Hare, J. P. *M Clin N Amer* **2** 1455, 1919. Rabinowitch, I. M., and Childs, M. C. C. Contribution to Biochemistry and Treatment of Chronic Nephrosis, *Arch Int Med* **32** 758 (Nov.) 1923. Mason, E. H. *Internat Clin* **1** 163, 36 series, 1926.

8 Bowen, B. D., and Boothby, W. M. *J Urol* **1** 469, 1917. Epstein, A. A., and Lande, H. (footnote 2).

9 Percy, J. F. Thyroid Extract in Nephritis, *J A M A* **59** 1708 (Nov. 9) 1912.

10 Percy, J. F. Nephritis. Its Treatment with Thyroid as a Preliminary to Operation, *J A M A* **61** 380 (Aug. 9) 1913.

11 Phipps, C. *Boston M & S J* **174** 73, 1916.

12 Bowen, B. D., and Boothby, W. M. *J Urol* **1** 469, 1917.

13 Eppinger, H. *Zur Pathologie und Therapie des menschlichen Odems*, Berlin, 1917.

persons and experimental animals thyroid extract appeared to diminish the ability of the cells to hold water and salts, so that these substances were returned to the blood and excreted at an increased rate. On the other hand, extirpation of the thyroid gland resulted in increasing the storage of water and salts in the tissues, and in consequent slowing of the rate of excretion. In the therapeutic use of thyroid extract, striking results were obtained in cases of edema in chronic parenchymatous nephritis. Eppinger is convinced that the beneficial results of thyroid extract are due to its effect on the cellular metabolism, and believes that they suggest an association of hypothyroidism and edema. Epstein, on the same basis, also recommends thyroid extract as a supplement to his treatment of nephrosis with high protein diet.

Although Eppinger and Epstein are strong advocates of thyroid therapy in nephrosis, its use has not found general acceptance. I shall report the effect of oral administration of thyroid extract in two cases of nephrosis which conform to the definition of Epstein both clinically and in the blood and metabolic observations.

REPORTS OF CASES

CASE 1—Y. H. T., a Chinese man, aged 42, was admitted to the Peking Union Medical College Hospital on May 22, 1926, with a history of a gradual onset of edema of the face and lower extremities five weeks prior to admission. This was followed by swelling of the scrotum and abdomen, with oliguria and dyspnea. There was no history of infection previous to the onset. Examination revealed generalized subcutaneous edema with moderate ascites and a small effusion into the pleural sacs and tunica vaginalis. The body weight was 60 Kg., and the height, 160.6 cm. The temperature was normal, the pulse rate, 60. No foci of infection were found in the throat, ears, sinuses or teeth. The eyegrounds were normal. The blood pressure was, systolic, 150, diastolic, 80. The urinary output was from 500 to 700 cc a day. There was marked albuminuria, about 20 Gm per liter of urine, with many hyaline casts, and only an occasional red blood cell in the urine. The phenolsulphonphthalein output in two hours was 15 per cent. The blood picture showed slight secondary anemia with a normal number of white blood cells in the usual distribution. Blood chemistry figures were as follows: nonprotein nitrogen, 37 mg; uric acid, 5.3 mg; creatinine, 1.6 mg; carbon dioxide capacity, 44.7 per cent by volume; cholesterol, 400 mg; albumin, 3 per cent, and globulin, 15 per cent. The basal metabolism as determined with Tissot's spirometer was -18.7 per cent.

For three weeks after admission, the patient was given magnesium sulphate and a low protein and low salt diet, with fluids limited to 1,000 cc, there was no visible change in the edema and the body weight remained stationary (fig. 1). Thyroid therapy was commenced, first with 0.24 Gm of dried thyroid gland daily for five days (June 14 to 18), then with 0.36 Gm daily for nineteen days (June 19 to July 7). During this period, there was a rapid discharge of edema, the body weight decreasing from 60 Kg to 46 Kg. The basal metabolism rose from -18.7 to -7 per cent, the blood cholesterol fell from 400 mg to 240 mg, the albumin content became 2 per cent and globulin 2.4 per cent. During the following period (July 8 to 24), in which thyroid medication was continued, the basal metabolism showed a further rise to $+16.4$ per cent, the blood cholesterol showed a further fall to 200 mg, albumin increased to 2.6 per cent and globulin to 4 per cent. There was, however, a tendency to reaccumulation of

edema, which was especially marked on the discontinuance of thyroid extract (July 25 to August 1) At the end of this period of withdrawal of thyroid medication, the basal metabolism fell to -14.1 per cent, and the blood cholesterol again increased to 400 mg

It was then decided to give intensive doses of thyroid extract a trial (0.96 Gm daily for four days, August 2 to 6) The resulting discharge of edema was spectacular The urinary output increased to 3,000 cc per day, and the body weight decreased from 51.8 Kg to 42.7 Kg, a decrease of 9 Kg in four days The basal metabolism increased rapidly to $+17.1$ per cent, the blood cholesterol decreased to 343 mg, the albumin content was 25 per cent and globulin 27 per cent Apparently the changes in the blood were slower than

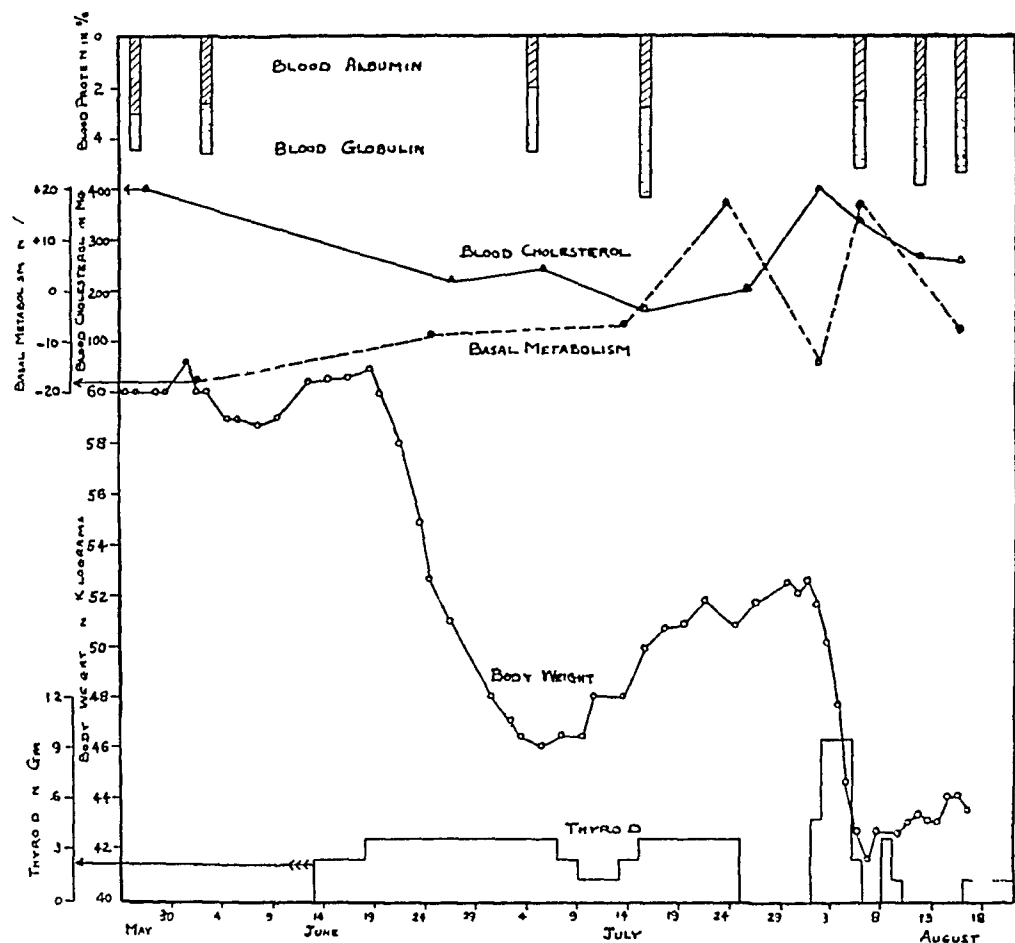


Fig 1 (case 1)—Effect of thyroid medication on body weight (edema), basal metabolism, blood cholesterol and blood proteins in nephrosis

those in the basal metabolism There was slight palpitation of the heart with tachycardia and emotional disturbances with increased mental irritability, which, however, disappeared promptly when thyroid medication was discontinued temporarily and then given in small doses In regard to the urinary observations at the end of this period, albuminuria was reduced to 0.5 to 1 Gm per liter with only a few hyaline casts and with a phenolsulphonphthalein output of 40 per cent in two hours The blood pressure was 128 systolic and 64 diastolic Edema was not demonstrable anywhere in the body

CASE 2—Y C S, a Chinese woman, aged 41, married, was admitted to the Peking Union Medical College Hospital on May 11, 1926, on account of anasarca, accompanied by oliguria and frequent vomiting, with an insidious onset fifteen weeks before admission There was a history of "cold" with cough and fever

for ten days shortly before the onset of edema. She had had six pregnancies, the last one a year before, edema had not been noticed during any of the pregnancies. Physical examination confirmed the patient's statement about the generalized edema with moderate ascites, but hydrothorax was not present. She was mentally dull and apathetic, with normal temperature. The body weight was 64.8 Kg, the height, 144 cm. Her throat, sinuses, ears and teeth did not show any signs of infection. Her eyegrounds were normal. The thyroid gland was not palpable. The heart was of normal size with a blood pressure of 118 systolic and 62 diastolic. The lungs showed slight dulness at the bases. Urinalysis showed marked albuminuria, 10 Gm per liter, many granular and hyaline casts and no red blood cells. The urinary output amounted to 500 cc

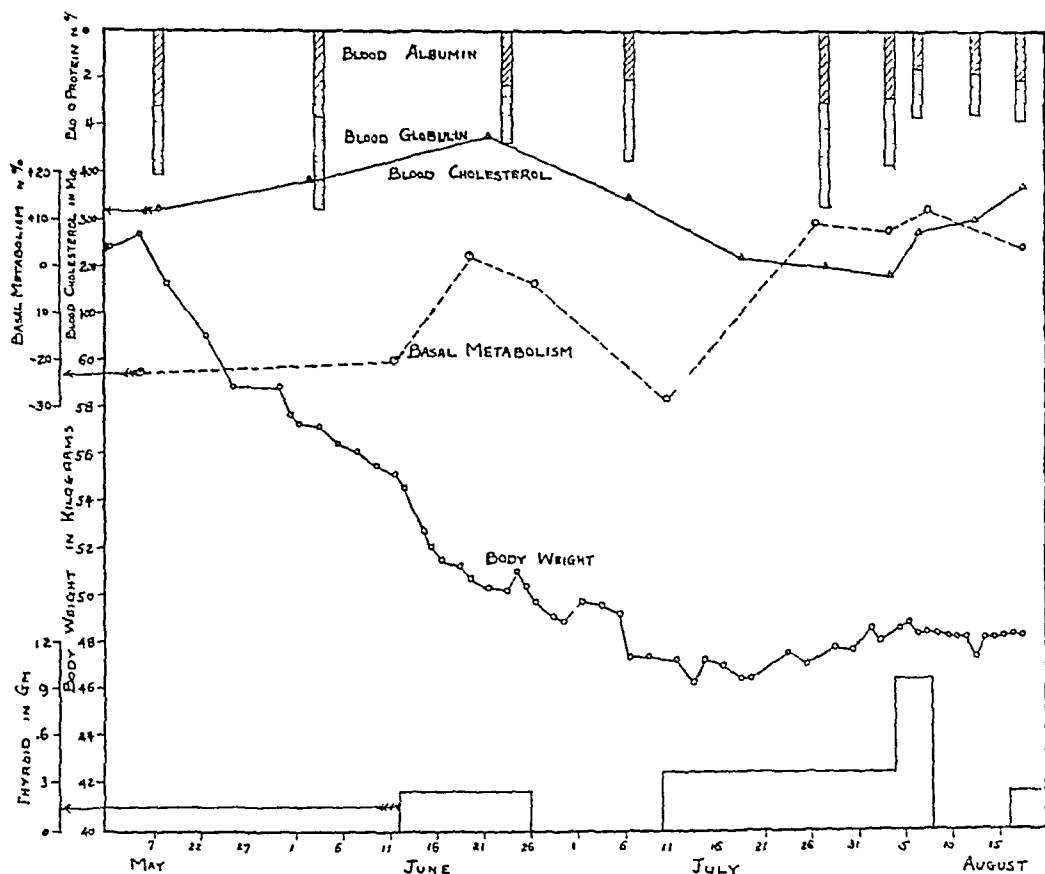


Fig 2 (case 2) —Effect of thyroid medication on body weight (edema), basal metabolism, blood cholesterol and blood proteins in nephrosis

a day with a phenolsulphonphthalein excretion of 18 per cent in two hours. Examination of the blood revealed a slight secondary anemia and no leukocytosis. The blood nonprotein nitrogen was 40 mg, cholesterol 320 mg, albumin 32 per cent and globulin 3 per cent. The basal metabolism was -23.5 per cent.

Rest in bed, a diet low in protein and in salt, and the use of mild saline catharsis caused her edema to decrease gradually, and in thirty days (May 13 to June 11) her body weight was reduced from 64.8 Kg to 55.3 Kg (fig 2), with slight subjective improvement. Toward the end of this period when the discharge of edema had slackened, small doses of thyroid extract were given for two weeks (0.24 Gm a day from June 12 to 15). The thyroid extract raised her basal metabolism to normal, and caused a slightly accelerated discharge of edema and marked subjective improvement with return of appetite and brightening of mentality, although the cholesterol value became higher and

the protein lower. Then thyroid treatment was stopped for two weeks (from June 26 to July 9), at the end of which period her basal metabolism showed a rapid fall to -29 per cent, followed by a prompt rise to $+10$ per cent on the resumption of thyroid treatment in a dosage of 0.32 Gm per day for twenty-five days (from July 10 to August 3). During this period of thyroid administration when the basal metabolism was elevated, edema did not recur, the blood cholesterol decreased, and the blood proteins increased until they reached approximately normal levels.

Large doses of thyroid extract (0.96 Gm per day for four days from August 4 to 7) were followed by a moderate tachycardia without further marked increase in the basal metabolic rate. The blood cholesterol, however, was unexpectedly high and proteins unexpectedly low at this time. The albuminuria, however, decreased considerably, and casts disappeared from the urine. The phenol-sulphonphthalein output in two hours was 20 per cent. The blood pressure was 114 systolic and 62 diastolic. At the time of this report the patient is receiving a dose of thyroid extract calculated to replace its excretion. She does not complain, and edema has not recurred.

COMMENT

The two cases reported represent fairly typical examples of Epstein's chronic nephrosis with rather gradual onset of generalized edema. The blood pressure was slightly raised in one case, but normal in the other. Cardiac enlargement and changes in the eyegrounds did not occur in either case. The urine showed pronounced albuminuria and moderate cylindruria, with diminished output and low phenolsulphonphthalein excretion. There was no retention of nonprotein nitrogen. The high blood cholesterol, the low plasma protein with inversion of albumin-globulin ratio, together with the depressed basal metabolism, complete the picture of nephrosis. A secondary anemia was present in both cases.

After the administration of thyroid extracts, in small doses at first and large doses later, the disappearance of edema in case 1 was striking. The reduction of albuminuria was equally striking in this case. The result in case 2 was not so spectacular. The decrease of edema was only slightly more rapid after the thyroid treatment, but the general subjective improvement was unmistakable.

In regard to the diuretic effect of thyroid in nephrosis, nothing definite can be said concerning its mode of action. From the observations made in the cases reported with an increase of basal metabolic rate following thyroid ingestion there were definite changes in the blood cholesterol and proteins. With the exception of one or two unaccountable variations, a rise of basal metabolism was usually followed by a fall in blood cholesterol and a tendency to rise in blood proteins. Sometimes the changes in the blood were not so rapid as those in the basal metabolic rate. Whether Epstein's theory that the edema in nephrosis is due to decreased blood protein, thereby allowing a free transudation of blood fluids into the tissues, finds confirmation here cannot be stated, as the correlation between blood proteins and edema in these two cases is not complete enough to justify a conclusion.

The inverse variation between basal metabolism and blood cholesterol noted in these two cases has also been found in diseases of the thyroid.⁵ Blood cholesterol is low in hyperthyroidism, while in myxedema it is high. With a decrease of basal metabolism in hyperthyroidism following treatment, cholesterol values also rise. While the changes in cholesterol may be secondary to the action of thyroid extract, they may serve as an indication of thyroid activity and the level of basal metabolism in disease of the thyroid and in nephrosis, and possibly in other conditions.

The etiology of the two cases of nephrosis reported in this article is obscure. "Cold" before onset was admitted in one case, but no history of infection was obtainable in the other, and careful examination failed to reveal any foci of infection in either case. Pregnancy apparently did not enter into the etiology. On the other hand, the beneficial results of thyroid treatment in such cases cannot be taken to indicate an etiologic relationship between thyroid deficiency and nephrosis, because the benefit obtained is not as complete as one would expect if it were a frank case of replacement glandular therapy as in myxedema. Nevertheless, as symptomatic treatment in nephrosis, thyroid medication is useful and to be recommended.

SUMMARY AND CONCLUSIONS

- 1 Two cases of nephrosis are reported in which the effects of thyroid medication were observed.

- 2 Thyroid therapy caused rapid disappearance of edema in one case, and accelerated discharge of edema in the other case when this slackened under ordinary eliminative treatment. In both cases there was subjective improvement and reduction of albuminuria. The data obtained, however, do not warrant the conclusion that nephrosis is dependent on a hypothyroid state.

- 3 With a rise of basal metabolism following thyroid administration, there was a decrease of blood cholesterol and a tendency of blood proteins to increase.

THE ARTERIOLAR LESIONS OF GLOMERULO- NEPHRITIS *

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It has been known since the time of Gull and Sutton¹ that lesions of the arterioles are present in many cases of arterial hypertension. In a previous communication² I presented the results of a study of the arteriolar lesions of essential hypertension. Under this term were included the numerous—and probably etiologically diverse—"cases of chronic hypertension which neither clinically nor anatomically can be demonstrated to have evolved from antecedent inflammatory disease of the kidneys or from urinary obstruction." It was concluded that the arteriolar lesions (arteriosclerosis) occurring in essential hypertension result from the increased wear and tear incidental to the hypertension, being a pathologic exaggeration of similar, though slighter, changes in the arterioles which are a physiologic accompaniment of advancing years.

If the view that the arteriosclerotic lesions are the result of the hypertension is correct, it would be expected that these lesions would be found not only in essential hypertension but also in the other great group of cases of chronic hypertension, namely, diffuse glomerulonephritis, in which there may be arterial hypertension lasting for many years. With this in mind, the arterioles of various organs were examined in thirty-seven cases of diffuse glomerulonephritis in different stages. The arteriolar lesions occurring in diffuse glomerulonephritis are of four anatomically and pathogenetically distinct varieties: (1) necrotizing arteritis, (2) endarteritis obliterans, (3) arteriosclerosis and (4) hypertrophy of the muscular layer. Each of these will be considered separately.

NECROTIZING ARTERITIS

Acute inflammatory and necrotizing processes in the arterioles of the kidney in acute and subacute glomerulonephritis have been described by Loehlein,³ Baehr and Sacks,⁴ and Jaffe.⁵ According to Loehlein,

* From the Laboratories of the Mount Sinai Hospital.

1 Gull and Sutton. On the Pathology of the Morbid State Commonly Termed Chronic Bright's Disease, *Tr Medico-Chir Soc Edinburgh* **55** 273 1872.

2 Fishberg. Anatomic Findings in Essential Hypertension, *Arch Int Med* **35** 650 (May) 1925.

3 Loehlein. Ueber die entzündlichen Veraenderungen der Glomeruli der menschlichen Nieren, Leipzig, 1907, cases 16, 17 and 27, Ueber Schrumpfnieren, *Beitr z Path Anat u z allg Pathol* **63** 570, 1917.

4 Baehr and Sacks. The Occurrence of Glomerulonephritis in Association with Verrucous Endocarditis, *Proc New York Path Soc* **23** 64, 1923.

5 Jaffe. The Vascular Changes of the Kidney in Hypertension, *Am J M Sc* **179** 88 (Jan) 1925.

these acute arteriolar changes are not found in the first stage of acute glomerulonephritis, but occur in severe form in from 10 to 20 per cent of the cases of late acute and early subacute glomerulonephritis. Slight arteriolar lesions are more common at this period. Baehr and Sacks found that these arteriolar lesions are particularly frequent in glomerulonephritis associated with verrucous endocarditis. They describe five such cases.

The nature of the lesions is illustrated in the following case.

CASE 1—History—Max S., aged 33, was admitted to the Mount Sinai Hospital on March 3, complaining of fever, malaise and cough. His past history was irrelevant. His illness started on February 10 with a severe "cold in the head." After suffering from sore throat, headache, chilly sensations and general weakness, he went to Bellevue Hospital, where a diagnosis of pneumonia was made. He developed facial erysipelas while there and was discharged eleven days after entrance. After this he was told by a physician that he had kidney trouble, fever and cough were still present.

Examination—On entrance the patient seemed to be acutely ill. There was erythema of the nose, cheeks and forehead resulting from erysipelas. Examination of the organs of the head revealed acute nasopharyngitis as well as a perforation of the right ear drum. There were signs of consolidation at the right base. Purpuric spots were present over the groins and feet.

The blood pressure was 104 systolic and 68 diastolic.

The specific gravity of the urine was between 1.010 and 1.018 during the patient's stay in the hospital. Albumin was always present, increasing progressively in amount. Hyaline and granular casts and white and red blood cells were abundant, at times the urine was macroscopically bloody.

Examination of the blood showed hemoglobin, 68 per cent, red blood cells, 3,840,000, white blood cells, 15,600, polymorphonuclear neutrophils, 66, eosinophils, 1, lymphocytes, 29, myelocytes, 2 per cent, and platelets 240,000. The Wassermann reaction was negative.

When the patient entered the hospital, the blood chemistry revealed urea nitrogen, 32.2, nonprotein nitrogen, 52.5, uric acid, 4.8 and creatinine 1.7 mg per hundred cubic centimeters. The nitrogenous bodies rose progressively until the following figures were attained: urea nitrogen, 107.8, nonprotein nitrogen, 228.4, uric acid, 9, and creatinine, 6 mg per hundred cubic centimeters.

The temperature was normal on admission but then rose, at times being as high as 104 F.

Course of Illness—The patient's course was progressively downward. Signs of fluid in the left pleura appeared, and there was evidence of bronchopneumonia in the right lower lobe. The purpura became widespread. The patient became comatose, and died on March 10.

Necropsy—There was no edema. The heart was not enlarged, weighing 360 Gm. The aorta had but a few patches of atherosclerosis, and the elasticity was excellent. The left pleura contained 700 cc of pus. There were a few bronchopneumonic patches in the lower lobes. The spleen was slightly enlarged, weighing 140 Gm.

The kidneys were greatly enlarged, weighing 760 Gm. The capsule stripped with moderate difficulty, revealing a pale, yellowish-brown surface, speckled at intervals by minute hemorrhages. On cut section, the parenchyma was pale yellow. The cortical markings were totally obliterated.

Microscopically, the architecture was well preserved. Most of the glomeruli were enlarged. The capillary loops were either completely or nearly completely devoid of blood. The number of nuclei in the tufts was greatly increased, this being due to the proliferation of what seemed to be endothelial nuclei. There

were few polymorphonuclear leukocytes in the loops, and the lumens were largely blocked, either by the presence of an amorphous substance or by the swelling of the endothelial cells. The cells of the parietal layer of Bowman's capsule were swollen and often desquamated, in some of the glomeruli they had proliferated so as to form small epithelial crescents consisting of three or four layers of epithelial cells. In Bowman's capsule there were often desquamated epithelial cells, red and white blood cells and coagulated exudate. There were a few capsular adhesions. In some of the glomeruli there were granular areas of necrosis in which nuclear staining was absent. The tubular epithelium showed marked regressive changes, the proximal convoluted tubules being particularly involved. Some of the nuclei did not stain. The cytoplasm was filled with hyaline droplets. The sudan stain showed numerous tiny fat droplets at the base of the cell. The lumens of the tubules contained numerous red and white blood cells and casts. There was abundant hemorrhage into some of the tubules.

The vasa afferentia were often greatly dilated, sometimes having the "lake-like" appearance described by Loehlein. In many places there were small necroses, the nuclei not being visible and the protoplasm stained a smudgy dark red. In some areas the vessel wall had been infiltrated by mononuclear cells, and there were unstained spaces between the loosened tissue elements. In a few of the vasa afferentia the lumen was occluded by swelling of the walls, but this was not a marked feature. There were tiny perivascular infiltrates of mononuclear cells around some of the vasa afferentia at their entrance into the glomeruli. In the interlobular vessels, the chief lesion was in the media. Here the muscle cells were often separated by unstained areas. The muscle cells themselves often appeared granular, and many of their nuclei were pyknotic, some of the nuclei apparently did not stain.

The entire duration of the patient's illness was one month. Whether the glomerulonephritis was due to the throat infection, the pneumonia or the erysipelas, cannot be said. The extreme severity of the renal process is shown by the fact that in less than one month it led to renal insufficiency and death in uremia. The histologic picture also demonstrates the acuteness of the changes, only acute inflammatory, degenerative and necrotizing processes were present, and there was no evidence of repair.

Of eight patients with severe acute diffuse glomerulonephritis examined, three presented acute necrotizing arteritis of the type described in the aforementioned case. In one instance associated with acute verrucous endocarditis (probably rheumatic), previously studied by Baehr and Sacks, the arteriolar lesions differed from those in the case presented in that hyaline thrombosis of the necrotized vasa afferentia was the outstanding histologic finding, this thrombosis often extended into the glomerular capillaries. In an instance of severe acute glomerulonephritis supervening in a patient with marked cardiac hypertrophy and apparently hypertension of long standing, the changes in the renal arterioles were similar to those in the case described in the foregoing. Arteriolar lesions of any considerable severity were not found in five cases.

The lesions in my cases were not so severe as in those of Loehlein. In some of his cases the necrosis of the arteriolar walls was so extreme that tiny aneurysms were formed, and blood escaped from the vessel into

the surrounding tissues. There was also complete obstruction of the lumen by detritus from the breakdown of the walls.

The case that I have described is of particular significance for the pathogenesis of the arteriolar lesions since there was no arterial hypertension, as is present in most cases of severe acute nephritis, presumably because the poor general condition of the patient impaired the functional ability of the heart. Acute arteriolar lesions (arteritis and arterionecrosis) are therefore not due to the mechanical factor of arterial hypertension and must be considered as toxic in origin. It seems probable, as Loehlein believes, that arteriolar lesions are to be attributed to the same agent that produces glomerulonephritis, the arteriolar lesions being part of the glomerulonephritis.

It is not known why the arterioles of the kidney are so severely injured in some instances of acute glomerulonephritis, while in the majority of cases they are not impaired. Baehr and Sacks believe that in the cases of acute glomerulonephritis described by them in which there were severe arteriolar lesions associated with acute verrucous endocarditis, but in which no Aschoff bodies could be demonstrated, the virus must have been "endotheliotropic," affecting the glomerular capillaries, endocardium and renal arterioles. Until there is more adequate information as to the etiology of glomerulonephritis, however, these questions can be discussed only hypothetically.

It does not seem probable that the necrotizing arteritis of acute glomerulonephritis has any relation to the arteriolar lesions found in chronic glomerulonephritis. These acute arteriolar lesions occur, so far as is known, only in severe cases, and it is improbable that many of the patients survive long enough for the disease to reach the chronic stage. The arteriolar lesions of chronic nephritis occur in many cases in which there is no history of a severe acute nephritis of the type in which necrotizing arteritis is found.

Inflammatory and necrotizing lesions of the renal arterioles similar to those just described in acute nephritis are seen on rare occasions in severe and rapidly progressive cases of essential hypertension. Such cases were first described by Fahr,⁶ who termed the condition malignant sclerosis. Similar cases have been described by Herxheimer⁷ and Stern⁸ who designated the condition as arteriolo-necrosis. These lesions usually occur in young adults. Fahr believes that these cases are of special etiology, he described instances due to lead, rheumatic fever and syphilis.

6 Fahr. Ueber Nephrosclerose, *Virchows Arch f path Anat* **226** 119, 1919

7 Herxheimer. Ueber Arteriolinekrose der Nieren, *Virchows Arch f path Anat* **251** 709, 1924

8 Stern. Ueber einen besonders akut verlaufenen Fall von Arteriolinekrose der Nieren, *Virchows Arch f path Anat* **251** 718, 1924

ARTERIOULAR LESIONS IN CHRONIC GLOMERULONEPHRITIS

In essential hypertension the lesions of the arterioles of the kidneys and certain other organs are all of the type termed arteriosclerosis, which is indicated by strong evidence to be a manifestation of the increased strain to which the arterioles are subjected by hypertension² In chronic glomerulonephritis either arteriosclerosis or endarteritis obliterans may be present, the frequency of the latter lesion having been indicated only comparatively recently by Volhard⁹ When the pathogenesis and significance of the arteriolar lesions are considered, it is necessary that arteriosclerosis and endarteritis obliterans be sharply differentiated

In his fundamental investigations on arteriosclerosis, Jores¹⁰ showed that there are two chief varieties of diffuse thickening of the intima of the arteries In the variety which he termed hyperplastic intimal thickening, the basis of the intimal thickening is a hyperplasia of the internal elastic membrane which splits into a number of thick interwoven layers, these often undergo fatty change Hyperplastic intimal thickening is seen distinctly in the interlobular arterioles of the kidney in essential hypertension The other variety of diffuse intimal thickening is termed by Jores regenerative connective tissue proliferation of the intima Here the basis of the intimal thickening is the proliferation in the intima of ordinary (collagenous) connective tissue, the internal elastic membrane not becoming hyperplastic If elastic tissue is formed in the intima, it is deposited in the form of fine fibrils in the midst of the collagenous fibers, but the basis of the process is the formation of collagenous connective tissue in the intima Regenerative connective tissue proliferation is the variety of intimal thickening that occurs when a vessel is ligated and when there is physiologic obliteration of vessels, such as the umbilical vein

Hyperplastic intimal thickening forms the anatomic basis of arteriosclerosis and arteriosclerosis in vessels of the size of the interlobular arterioles of the kidney or larger, regenerative connective tissue proliferation is the variety of intimal thickening seen in endarteritis obliterans It is usually easy to differentiate arteriosclerosis and endarteritis obliterans in vessels the size of the interlobular arterioles of the kidney in which the elastic hyperplasia in arteriosclerosis is striking, but this is sometimes more difficult or impossible in the case of the vasa afferentia near their entrance into the glomerulus In these arteriosclerosis is usually manifested solely by subendothelial deposition of hyaline substance, and precisely the same appearance can be

⁹ Volhard Mohr and Staehelin's *Handbuch der inneren Medizin*, Berlin
3 1519, 1918

¹⁰ Jores *Wesen und Entwicklung der Arteriosklerose*, Wiesbaden, 1903

secondarily produced in endarteritis obliterans of these tiny vessels by the frequently occurring hyaline degeneration of the proliferated connective tissue of the intima. Fatty change may occur in either variety of intimal thickening.

I have studied the arteriolar lesions in various organs of the body in twenty-nine cases of chronic diffuse glomerulonephritis. In all these instances the renal process had been of considerable duration, as evidenced histologically by the presence of hyalinization of the glomerular loops or glomerular or interstitial fibrosis. In these cases various stages of the condition were represented, they ranged from some that might perhaps with equal justice have been termed "subacute" to instances of secondary contracted kidney of many years' duration. No examples of diffuse glomerulonephritis occurring in subacute bacterial endocarditis, as described by Baehr and Lande,¹¹ are included in this group of twenty-nine cases.

ENDARTERITIS OBLITERANS

Endarteritis obliterans of greater or less extent was present in the arterioles of the kidney in seventeen of the twenty-nine cases of chronic diffuse glomerulonephritis. The following case will serve as an example of those in which the endarteritis obliterans was of high degree.

CASE 2—History—Helen P., aged 26, was admitted to Mount Sinai Hospital on November 7, complaining of nausea and vomiting of two weeks' duration. There was nothing noteworthy in the personal or family history. About two years prior to admission she became ill with a severe sore throat accompanied by generalized pains in the body and fever, which lasted several weeks. Her tonsils were removed, and she felt somewhat better. About a year and a half before entering the hospital, she had a severe dental infection requiring the extraction of several teeth. Following this, headache and swelling of the ankles appeared, to which were soon added retrosternal pain, dizziness and marked weakness. During the seven months prior to admission, she urinated three or four times a night. Dyspnea and vomiting appeared about two months before entrance, but became severe during the last two weeks.

Examination—The patient was a well developed and well nourished young woman who was exceedingly restless. Her breath had a urinous odor. There was slight pretibial edema.

The heart was enlarged to the left. The second sound was accentuated at the aortic area. The pulse was of high tension, but thickening of the vessel wall could not be detected by palpation. The blood pressure was 230 systolic, and 120 diastolic. The urine had a specific gravity of 1.010, albumin was present, as well as a few red and white blood cells, but there were no casts. The blood chemistry was: urea nitrogen 81.2, nonprotein nitrogen 129.9, uric acid 8.5, creatinine 7, cholesterol 176 and sugar 155 mg per hundred cubic centimeters.

Course of Illness—During the patient's stay in the hospital large volumes of fluids were given, but despite this the daily urinary volume averaged but 25 cc. The patient became comatose and died twelve days after entrance.

Necropsy—The skin was waxy white. There was edema of the lower extremities. The lungs also were somewhat edematous.

¹¹ Baehr and Lande. Glomerulonephritis as a Complication of Subacute Streptococcus Endocarditis, J A M A 75 789 (Sept 18) 1920.

The pericardium contained 500 cc of clear, straw-colored fluid. There was a fibrinous exudate on the pericardium. The heart was enormously hypertrophied, weighing 790 Gm. The muscle of the left ventricle was 2 cm thick, that of the right 5 mm.

The right kidney weighed 120 Gm. It was slightly smaller than usual. The capsule appeared opaque and gray, it stripped with some difficulty, revealing the slightly granular, deep reddish-brown surface of the kidney. Numerous punctate hemorrhages were scattered over the surface of the kidney. There were also a number of small depressions. On section the kidney was firm, deep purplish

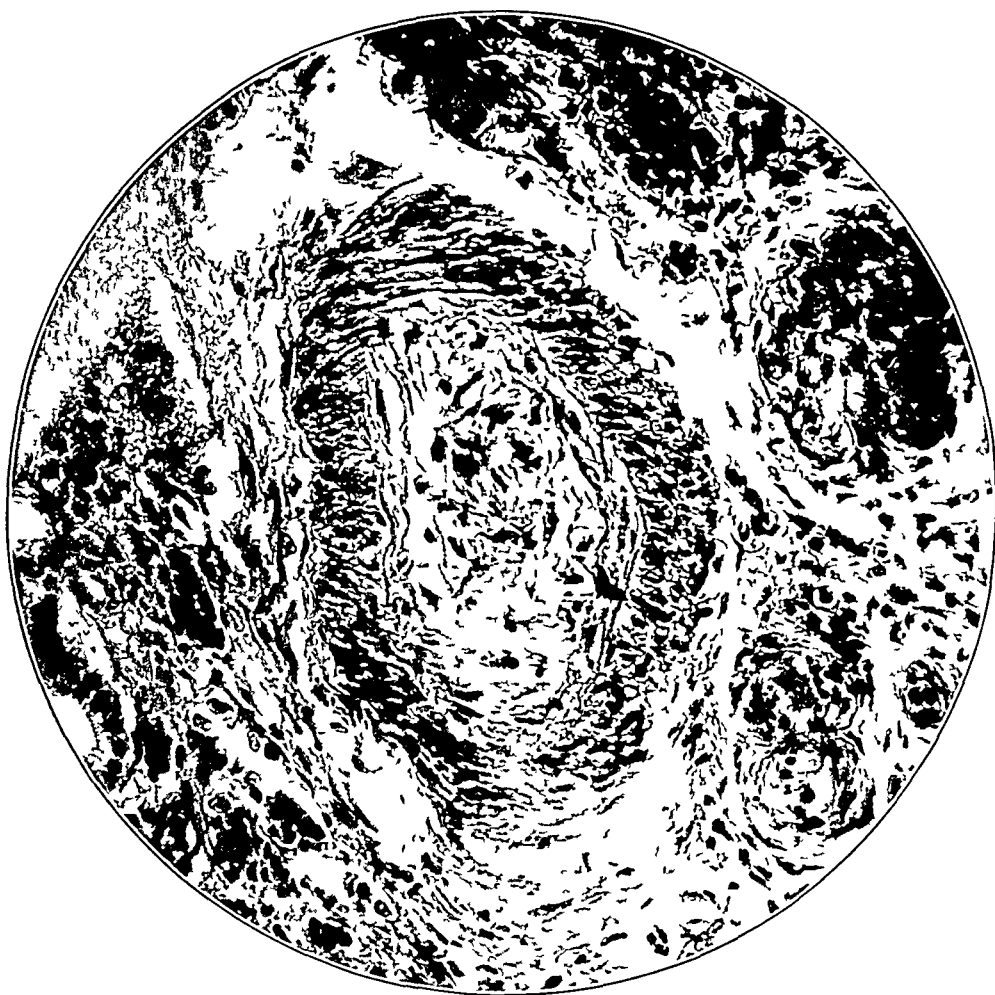


Fig. 1 (case 2) —Chronic glomerulonephritis, endarteritis obliterans completely occluding the lumen of an interlobular arteriole. There is no hyperplasia of the internal elastic membrane. The media is rather thick.

brown and showed an irregular thinning of the cortex and a number of scattered hemorrhages. The left kidney weighed 40 Gm and was about half the size of the right. The ureter on this side had an anomalous implantation, otherwise, the left kidney was similar to the right.

Histologically, it was seen that the architecture of the kidney was severely disturbed. Over large areas the tubules had collapsed or disappeared, and the interstices were filled in by granulation tissue rich in capillaries and mononuclear wandering cells, lymphocytes and young fibroblasts. The tubular epithelium showed severe degenerative changes. There were some islands of dilated tubules

lined by low epithelium, many of the tubules contained casts. There were some hemorrhagic areas. Some glomeruli were completely hyalinized and in various stages of shrinkage, most of the other glomeruli showed an increase in the number of nuclei in the tufts. The loops of some of the glomeruli were devoid of blood, in others, numerous red cells were found. The capillary walls were swollen and often diffusely hyalinized, particularly close to the entrance of the vas afferens. There was little proliferation of the epithelium of Bowman's capsule but some pericapsular fibrosis and capsular adhesions.

Arterial vessels of all sizes—arcuate, interlobular and afferent—showed intimal thickening of the endarteritic type. In some it was slight, in others it had gone on to complete obliteration. The intimal thickening was largely due to the presence of connective tissue between the internal elastic membrane and the endothelium, there was often also endothelial proliferation in the vasa afferentia. In most vessels the connective tissue appeared young, being rich in elongated nuclei, in others there were few nuclei. In places, the intima showed considerable fatty change. The internal elastic membrane was not hyperplastic, though in some of the vessels thin strands of elastic tissue were visible in the thickened intima. The intimal thickening was by no means always uniform around the vessels, so that in some the lumen was eccentric, giving the appearance often seen in syphilitic endarteritis of the cerebral arteries. Only a few of the afferent arterioles showed hyalinization. The medial muscle layer in most vessels appeared normal, in some it was thicker than usual.

The arterioles of the heart, lungs, liver and suprarenals seemed normal, those of the spleen were perhaps somewhat more hyaline than is usual at this age.

As mentioned, well marked endarteritis obliterans was found in the kidneys of seventeen of the twenty-nine patients who had chronic diffuse glomerulonephritis. The frequency and degree of the endarteritis varied with the stage of the glomerulonephritis. There were three groups of cases.

- 1 In the six cases in which the histologic observations, confirmed in some instances by the clinical history, showed the renal disease to be of comparatively recent origin, endarteritis obliterans was either totally absent or of but slight degree.

- 2 Twelve of the cases were examples of the secondary contracted kidney, in these there was no active inflammatory process, only the final results of the glomerulonephritis were to be seen in the form of extensive areas of connective tissue containing some completely hyalinized glomeruli with atrophic tubules and areas of hypertrophied functioning glomeruli and tubules. In only three of these twelve cases was endarteritis a well marked feature, and in these there was considerable evidence of "activity."

- 3 In the other eleven cases the patients died while the inflammatory process in the kidney was still active, as manifested by the presence of nuclear proliferation and ischemia of the glomeruli, fatty, hyaline droplets and other degenerative changes in the tubular epithelium, hemorrhages, and other pathologic evidence. In all of these cases endarteritis obliterans was present, in five instances being as marked as in the case detailed in the foregoing, and distinct in all the others.

In practically all of these cases, the arterioles of the heart, lungs liver, spleen and pancreas were examined, and in many instances numerous other organs as well, but endarteritis obliterans was found only in the kidney. The only exception was the case of a 22 year old patient with secondary contracted kidney, in whom the arterioles of the heart showed well marked connective tissue thickening of the intima.

In view of the isolated occurrence of this observation in the many cases examined, it seems justifiable to attribute it to some local cause. Endarteritis obliterans occurring in chronic diffuse glomerulonephritis seems to be entirely confined to the arterioles of the kidney. It should be mentioned, however, that I did not have an opportunity to examine the vessels of the retina, for Volhard¹² states that typical endarteritis obliterans identical with that found in the kidney occurs in the retinal arterioles in cases of albuminuric retinitis.

What is the origin of the endarteritis obliterans that occurs so frequently in the renal arterioles in chronic glomerulonephritis? Until Volhard⁹ pointed out that the lesions are endarteritic, they were usually confused with the arteriosclerotic changes occurring in the kidney during essential hypertension. As endarteritis obliterans is absent in essential hypertension and is often missing in old secondary contracted kidneys in which hypertension is almost invariably a dominant symptom, it cannot be the direct result of hypertension, as arteriosclerosis is believed to be. Moreover, I have twice noted marked endarteritis obliterans in cases of chronic glomerulonephritis complicating pulmonary tuberculosis in which hypertension was slight.

Volhard⁹ explains the occurrence of endarteritis obliterans on the basis of his angiospastic theory of glomerulonephritis. He believes that a spasm of the renal arterioles causes not only the glomerular lesions but, if it lasts long enough, also the endarteritis as a reaction to the ischemia. Volhard's angiospastic theory has met with little support outside of his own clinic, and Fahr¹³ and others have adduced strong evidence against it.

That the endarteritis is not of "toxic" origin, as is sometimes vaguely stated, is rendered probable by the fact that it is confined to the arterioles of the kidney. Endarteritis obliterans histologically similar to that of chronic glomerulonephritis is often seen in arterioles in the midst of areas of granulation tissue, as in tuberculous or chronic pneumonic processes in the lung. While such a mechanism may be an accessory factor in the production of endarteritis obliterans in chronic glomerulonephritis, in which there is much interstitial reaction, that it

¹² Volhard. Ueber die Retinitis Albuminurica, Verhandl. d. deutsch. Gesellschaft f. inn. Med. **33** 422, 1921.

¹³ Fahr. Zur Pathogenese der akuten Glomerulonephritis, Deutsche med. Wchnschr. **52** 735 (April 30) 1926.

is not the primary cause of endarteritis obliterans can often be seen in arteries and arterioles that do not lie in areas of granulation tissue but are surrounded by urinary tubules

I have shown that endarteritis obliterans is not found in acute or early chronic glomerulonephritis, but occurs predominantly in cases in which, though they have lasted for several years, active destruction of glomeruli and tubules is still in progress. In these cases there is obviously great obstruction to or complete blockage of the blood current by the inflammatory process in the glomeruli. Since Thoma¹⁴ made his experiments, it is well known that when an artery is ligated or the blood stream otherwise slowed, endarteritis obliterans gradually appears, both proximal and distal to the ligature, and consists of connective tissue proliferation in the intima without hyperplasia of the internal elastic membrane. This is similar to the endarteritis that occurs in chronic glomerulonephritis, and it would seem that the cause of the endarteritis in this condition is akin to that in ligation experiments, namely, obstruction to the flow of blood. Endarteritis is not found in the renal arterioles in essential hypertension, because the arteriole is first thickened by arteriosclerosis with subsequent destruction of the glomerulus, while in glomerulonephritis the glomerulus is first injured, and the arteriolar changes follow.

The dependence of the arteriolar lesions on glomerular obliteration also explains why they are confined to the arterioles of the kidney and are absent in other organs. It further accounts for the frequent absence or minimal degree of endarteritis obliterans in most old cases of secondary contracted kidney. The glomeruli which become hyalized as the outcome of the inflammatory process gradually disappear completely. This can be seen in sections from some cases of chronic glomerulonephritis in which hyaline spheres representing obliterated glomeruli are found in sizes, varying from the size of normal glomeruli to tiny rests. In extreme examples of secondary contraction of the kidney (in one of my cases both kidneys weighed only 65 Gm.), it is obvious that by far the greater portion of the original glomeruli must have disappeared completely. The same fate must have befallen the arterioles leading to them, after closure by endarteritic intimal thickening. Intermediary stages of this process are to be observed in old cases of chronic glomerulonephritis, in which arterioles are often seen with the lumen completely closed by endarteritis and the originally thick medial muscle layer also being compromised on the other side by the surrounding granulation tissue.

14 Thoma. Das Verhalten der Arterien in Amputationsstumpfen, Virchows Arch f path Anat 95 294, 1884

It was mentioned in the foregoing that, according to Volhard, endarteritis obliterans occurs also in the retinal arterioles in albuminuric retinitis, which this author believes to be of angiospastic origin. He considers the ischemia produced by the angiospasm as the cause of both the retinal and the arteriolar lesions. It is interesting to note, however, that Leber,¹⁵ who has made the most exhaustive histologic studies of albuminuric retinitis, regards the endarteritis as secondary to the retinal changes, just as I consider the endarteritis in the renal arterioles secondary to the glomerular lesions.

ARTERIOLOSCLEROSIS

The histologic changes of essential hypertension were described in the foregoing. In a study² of seventy-two cases of essential hypertension, I found that in this condition the arteriosclerotic lesions are essentially identical in the organs in which they occur and have a characteristic distribution. They are always present in the kidney, having been found in every one of the seventy-two cases of essential hypertension mentioned. The splenic arterioles are affected in about two thirds of the cases, the pancreatic in about one half, the hepatic in less than one third and the cerebral in about one fifth. When lesions are present in the arterioles of these organs they are usually not nearly so marked as in the kidney. The terminal arterioles of the skin, skeletal muscles, myocardium, lungs, gastro-intestinal tract and thyroid are rarely involved, and then only to an insignificant extent.

I have found that arteriolosclerosis having the same distribution as that just described as essential hypertension occurs also in chronic glomerulonephritis. Similar observations have recently been reported by Branch and Linder,¹⁶ who noted lesions of the arterioles in six of seven young nephritic patients who died of uremia. The following case illustrates severe arteriolosclerosis in chronic glomerulonephritis.

CASE 3—History—Jacob L., aged 39, entered Mount Sinai Hospital on April 12, complaining of epistaxis, vertigo and dyspnea. Twenty years previously, he had been told by a physician that he had kidney trouble. A year ago he was in Mount Sinai Hospital because of hemiplegia on the left side, which cleared up almost entirely. For three weeks prior to admission the patient noticed that he was getting weaker, he was dyspneic and often dizzy and had several epistaxes. He also noted diminution in the acuity of vision.

Examination—The patient was well developed and well nourished. His breath had a urinous odor. Albuminuric retinitis was present. The heart was enlarged to the left, the first sound booming at the apex and the second sound accentuated and metallic at the aortic area. The radial arteries felt sclerosed and

¹⁵ Leber. Graefe-Saemisch-Hess's Handbuch der gesamten Augenheilkunde, ed 2, Leipzig, 7 803, 1915.

¹⁶ Branch and Linder. The Association of Generalized Arteriolar Sclerosis with High Blood Pressure and Cardiac Hypertrophy in Chronic Nephritis, J Clin Investigation 3 299 (Dec 20) 1926.

tortuous The blood pressure was 180 systolic and 110 diastolic The urine contained a large amount of albumin and a few casts

On entrance to the hospital the blood chemistry was urea nitrogen, 105, uric acid, 6, and creatinine, 7.6 mg per hundred cubic centimeters This rose to urea nitrogen, 135, nonprotein nitrogen, 191, uric acid, 11, and creatinine, 16 mg per hundred cubic centimeters Phenolsulphonphthalein excretion was almost nil in two hours

The patient became drowsy, gradually comatose, developed pericarditis and died with pulmonary edema on May 10

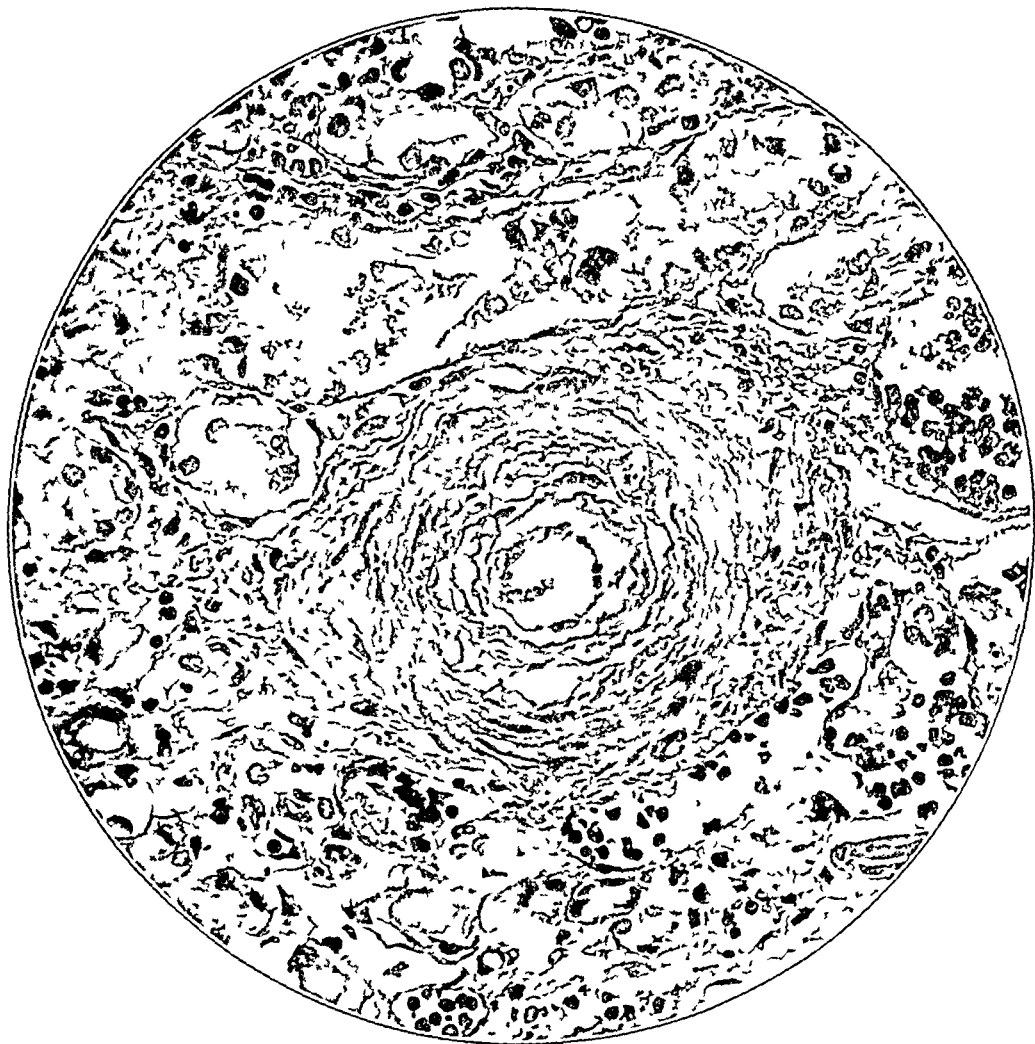


Fig 2 (case 3)—Chronic glomerulonephritis in the stage of the secondary contracted kidney Arteriosclerosis of an interlobular arteriole There is great hyperplasia of the internal elastic membrane The media shows atrophic changes

Necropsy—There was fibrinous pericarditis The left ventricle was greatly hypertrophied, the muscle being 2 cm in thickness The right ventricle was also hypertrophied

The right kidney was contracted The capsule stripped with great difficulty, revealing a pale, finely granular surface On section it was seen that the cortex was greatly thinned and the markings practically obliterated The kidney substance was firm and generally pale yellowish-brown The left kidney was in the pelvis to the left of the sacrum It was supplied by an anomalous branch arising from the aorta 3 cc above the bifurcation It was smaller than the right kidney but otherwise similar

Microscopically, no normal kidney tissue was seen. The kidney was almost entirely made up of large, irregular tubules lined by low epithelium and areas of edematous connective tissue infiltrated by numerous mononuclear cells. Only a few glomeruli were to be seen, and these showed nuclear proliferation and hyalinization of capillary loops. It seems astonishing that the excretory functions could have been carried on with so little renal parenchyma.

The arteries of all sizes were severely damaged. In most the intima was greatly thickened, sometimes to obliteration. The vasa afferentia showed hyalinization of the intima, which in many places had undergone fatty change. The interlobular and some afferent arterioles showed hyperplasia of the internal elastic membrane, so that interlacing strands of elastic tissue were to be seen. Between the elastic fibers there was a granular ground substance in which there were few nuclei. There was considerable fatty change in the intima. A few vessels showed thickening of the connective tissue of the intima, but this was not of high degree. The media was severely injured in vessels of all sizes. In some vessels it was still fairly thick, but there was a severe degenerative process of the muscle fibers, which appeared granular and often exhibited irregular or absent nuclear staining. Sometimes there were unstained spaces between the muscle fibers and irregular areas of fibrosis. In the majority of vessels the muscularis was greatly and irregularly thinned, so that in some places there was no muscle outside of the thickened intima. These atrophic and degenerative changes of the media were present in some vessels in which the intimal change was minimal.

The arterioles in the heart muscle of a size corresponding to the afferent and interlobular arterioles of the kidney appeared normal. Severe arteriolosclerosis was present in the arterioles of the pancreas and spleen, a lesser degree in those of the liver and suprarenals. The arteriolosclerosis in the pancreas was as marked as is seen in essential hypertension, in one of the pancreatic arterioles the intima was calcified, a rare observation in arteriolosclerosis.

Arteriolosclerosis was not found in any of the cases in the earlier stages of chronic glomerulonephritis. It was present in several of the moderately advanced cases, but to a mild degree. In all twelve cases of chronic glomerulonephritis in its final stage, the secondary contracted kidney, arteriolosclerosis was present. In some, the arteriolosclerosis was as severe as is found in essential hypertension of many years' duration, while in others it was much less marked.

It was found, moreover, that in these instances of chronic glomerulonephritis the distribution of the arteriosclerotic lesions was the same as that found in essential hypertension. That is, the lesions were always most severe in the kidney, the splenic and pancreatic arterioles were next most frequently and severely involved, and the liver, suprarenals and brain not so frequently. The arterioles of the heart and lungs (with the exception of the lungs in one case in which there was mitral stenosis) were only slightly involved, in the large majority of cases they were not affected. The single case in which endarteritis obliterans was present in the smaller radicals in the heart has been mentioned. The vessels of the gastro-intestinal tract, skin, voluntary muscles and thyroid, which were examined in a few cases, did not show any prominent lesions, usually being totally spared.

It is seen, then, that arteriolosclerosis identical in the structure and distribution of the lesions with that found in essential hypertension

occurs in cases of glomerulonephritis of long standing. Arteriosclerosis is not seen in early glomerulonephritis, and is but slight or absent in cases that have lasted but a few years, as in case 2.

The fact that arteriosclerotic lesions are found in cases of glomerulonephritis of long standing is strong evidence in favor of the view that these lesions are caused by arterial hypertension, for they are not found in early cases in which hypertension is already present, and usually already maximal, appearing only in the course of years, during which time the hypertension has persisted. It seems difficult to interpret these facts in any other way than that the hypertension causes the arteriosclerosis. Arteriosclerosis is thus a manifestation of long continued hypertension, whatever the origin of the latter. In a previous communication,² the fact was emphasized that arteriosclerotic changes of marked degree in the spleen and of relatively slight extent in the kidney are a physiologic accompaniment of advancing years, and that the arteriosclerosis of essential hypertension is to be regarded as a pathologic exaggeration of these physiologic changes resulting from the increased wear and tear of the hypertension. The occurrence in chronic glomerulonephritis of arteriosclerosis identical in structure and distribution with that of essential hypertension is added support for this view. Arteriosclerosis is thus a histologic symptom of chronic arterial hypertension.

The occurrence of marked arteriosclerosis in chronic glomerulonephritis must have deleterious consequences for the renal parenchyma, just as it does in essential hypertension. Volhard believes that endarteritis obliterans is responsible for the progression of the renal process in many cases of chronic glomerulonephritis. However, endarteritis obliterans is probably only of secondary importance in this direction, for the affected vessels are those which lead to glomeruli that are already functionally incapacitated. Arteriosclerosis, on the contrary, may affect vessels leading to intact glomeruli and lead to their destruction by cutting off the blood supply, precisely as occurs in essential hypertension. It seems probable that the arteriosclerosis resulting from the hypertension is partially responsible for the final renal insufficiency in many patients with secondary contracted kidney who die of uremia after many years of hypertension with intact renal function. The arteriosclerosis adds the coup de grace, so to speak, to the damage already wrought by the nephritic process.

MUSCULAR HYPERTROPHY

The existence of hypertrophy of the muscularis of the arterioles was first maintained by Johnson.¹⁷ Johnson's observations on medial muscu-

¹⁷ Johnson. On Certain Points in the Anatomy and Pathology of Bright's Disease, *Tr Medico-Chir Soc Edinburgh* 51: 57, 1868.

lar hypertrophy were later supported by the measurements of Ewald¹⁸ Subsequently, however, Jores¹⁹ pointed out that it is difficult to ascertain with certainty the thickness of the medial muscle because of possible postmortem contraction and other factors That there is an actual medial hypertrophy has been reaffirmed by Volhard,¹² who has also noted the absence of muscular hypertrophy in essential hypertension Baehr²⁰ has made similar observations

My observations on the muscular coat of the arterioles of the kidney in glomerulonephritis are as follows Neither in acute nor in the early stages of chronic glomerulonephritis are any changes in the medial musculature to be observed—with the exception of the necroses seen in some cases of severe acute glomerulonephritis as part of the necrotizing arteritis discussed in the first section In most cases of chronic glomerulonephritis of several years' duration, however, there is present a thickening of the medial muscle layer which is often marked and best seen in the interlobular and arcuate arterioles The following case is an example

CASE 4—*History*—Louis F, aged 14, entered Mount Sinai Hospital for the first time on Jan 22, 1921 Two weeks before he had suffered from sore throat which had kept him in bed a week Two days later the sore throat recurred, and with it appeared swelling of the face and hematuria On admission he was found to have the classical picture of acute diffuse glomerulonephritis with edema of the face, hypertension (180 systolic blood pressure and 100 diastolic), albuminuria, hematuria, and retention of nitrogen (urea nitrogen 60.2 mg per hundred cubic centimeters) During his stay in the hospital, which lasted two months, he had three convulsive seizures He was discharged feeling well During the next four years he went to school and worked In January, 1925, he reentered the hospital complaining of headache of two weeks' duration and nausea and vomiting for the past two days His blood pressure was 214 systolic and 160 diastolic, and he had retention of nitrogen He died of uremia ten days after admission In connection with the necropsy observations, it is interesting to note that Dr Eli Moschowitz, who had the patient under observation for a prolonged period, and to whom I am indebted for the clinical data, recognized that the evident thickening of the radial arteries was not due to sclerosis but to muscular hypertrophy and hypertonus

Necropsy—The heart was greatly enlarged, weighing 600 Gm Hypertrophy of the left ventricle was particularly marked

The left kidney weighed 80 Gm, the right 100 Gm The capsule stripped with difficulty, exposing a finely granular, yellowish-brown, mottled surface, dotted here and there with fresh hemorrhages The cortical markings were completely obscured The structural arrangement of the kidney was severely disturbed Large areas of granulation tissue were seen The tubules were mostly collapsed and contained casts, their epithelia showed various degenerative changes There were islands of enormously dilated and irregularly shaped tubules, showing efforts at regeneration No normal glomeruli were to be seen Most of them

18 Ewald Ueber die Veraenderungen kleiner Gefaesse bei Morbus Brightii, Virchows Arch f path Anat **71** 453, 1877

19 Jores Ueber die Arteriosklerose der kleinen Organarterien, Virchows Arch f path Anat **178** 374, 1904

20 Baehr, George Personal communication to the author

showed nuclear proliferation and blocking of the capillary loops. Some were completely hyalinized. There was hemorrhage into Bowman's capsule in a few, others showing capsular adhesions. There were no epithelial crescents.

Most of the interlobular and some of the afferent arterioles showed endarteritis obliterans, which in some was so marked as to close the vessel completely. The newly formed intimal connective tissue was rich in nuclei, in some vessels it was fatty. The elastica was normal in most vessels, in some there was slight hyperplasia. Many of the vasa afferentia showed marked hyalinization.

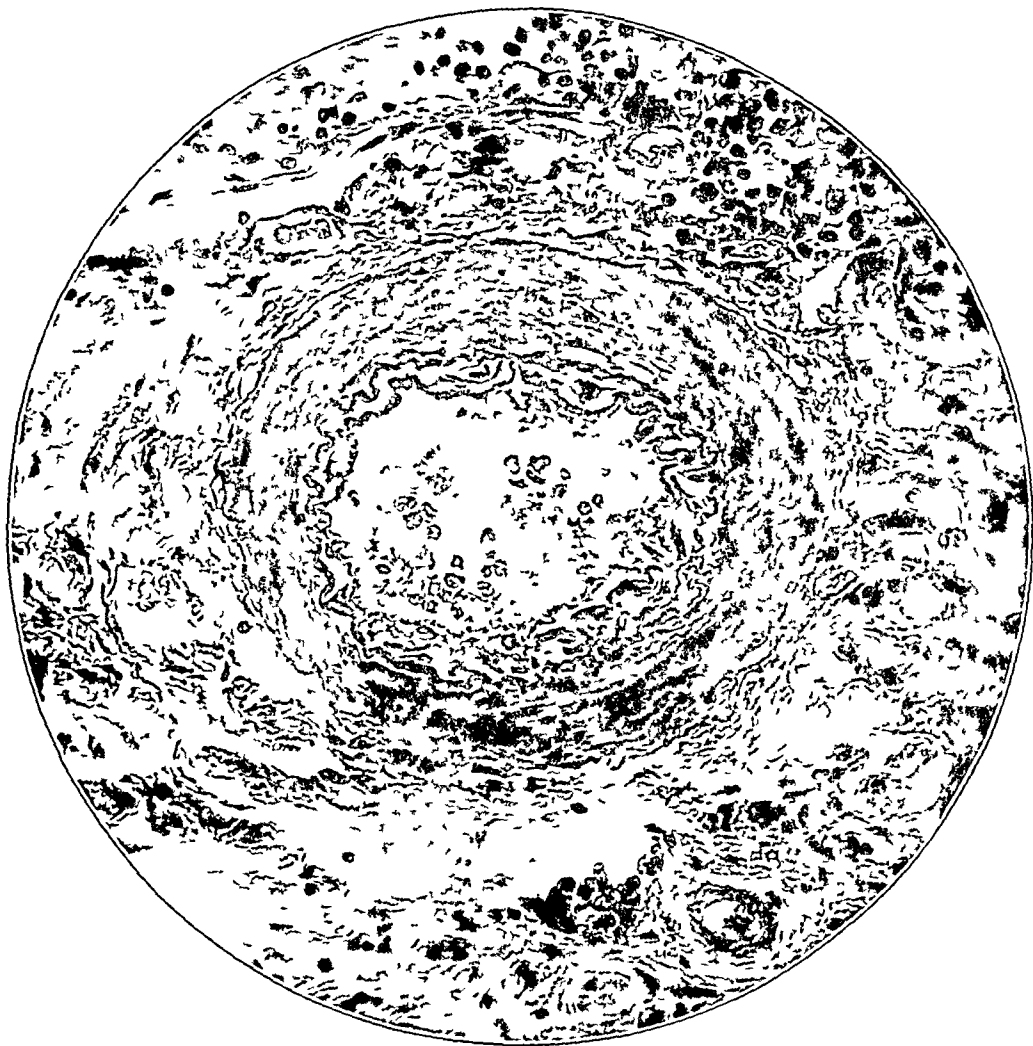


Fig 3 (case 4) —Chronic glomerulonephritis, interlobular arteriole showing medial hypertrophy in the absence of marked intimal thickening

On first examination of the section under low power magnification, many of the arterioles were strikingly prominent. This was due to the presence of a thick medial muscular layer, which was seen by comparison with similar sections of normal kidneys to be much thicker than usual. The thickening of the media was entirely muscular, the muscle cells lying close to one another without any fibrosis. The muscular thickening was best seen in the interlobular arterioles, but was also plain in the larger and smaller vessels. It was present in vessels with endarteritis obliterans as well as in a few without marked intimal thickening.

The arterioles of the heart, lungs, liver and spleen appeared normal. Some arterioles of the suprarenals seemed to have unusually thick medial muscle but this was not certain.

In some cases of old secondary contracted kidney the arterioles have a thick muscularis, but in others it is distinctly atrophied. Both hypertrophy and atrophy may be seen in different vessels of such a kidney, and sometimes it can be observed that a thick muscular layer is undergoing atrophy in places. The atrophy of the muscle in these cases is usually seen where there is well marked arteriosclerosis. In some vessels the atrophy is so marked that there remains only a thin layer of muscle cells outside of the thickened intima, and in places even this thin layer may be totally lacking.

The hypertrophy of the arteriolar muscle layer in the kidney is in most cases of chronic glomerulonephritis of several years' duration but still "active" is in direct contrast to the observations in essential hypertension in which atrophy of the medial muscle is the rule. Volhard believes that this medial hypertrophy is a manifestation of increased tonus of the renal arterioles in glomerulonephritis. It is interesting that when chronic glomerulonephritis lasts for many years and reaches the stage of secondary contracted kidney, the medial muscle atrophies. As these patients usually have arteriosclerosis, the same "anatomical picture" of the arterioles as in essential hypertension is often present—arteriosclerosis plus medial atrophy. It would thus seem that the effect of long continued hypertension is to produce finally medial atrophy as well as arteriosclerosis.

Definite hypertrophy of the media of the arterioles in organs other than the kidney was not found, though in isolated instances there were uncertain indications of it. The retina was not examined in any of the cases, however, Volhard states that medial hypertrophy is found in patients with albuminuric retinitis, the large vessels were not studied, but it is known that here also medial hypertrophy may be present (Fischer and Schlayer,²¹ Moschcowitz²²). Medial hypertrophy and increased tonus of the medial muscle are responsible for the impression of thickening given to the palpating finger by the radial artery in many cases of glomerulonephritis in which arteriosclerosis is absent. This condition has been termed pseudoarteriosclerosis by Moschcowitz.

SUMMARY

The arterioles of various organs were studied in thirty-seven cases of diffuse glomerulonephritis.

The arteriolar lesions of diffuse glomerulonephritis are of four histologically and pathogenetically distinct varieties.

1. Acute necrotizing arteritis was found in the renal arterioles in three of eight patients dying during the acute stage of diffuse glomerulo-

21 Fischer and Schlayer. *Die Arteriosklerose und Fühlbarkeit der Arterienwand*. Deutsches Arch f klin Med **97** 230, 1909.

22 Moschcowitz. Personal communication to the author.

nephritis. These lesions are probably of the same (toxic?) origin as the glomerular lesions.

2 Endarteritis obliterans was present in seventeen of twenty-nine cases of chronic diffuse glomerulonephritis in various stages. Endarteritis obliterans was not found in the early stages or often in the end stage (secondary contracted kidney). It occurred predominantly in those patients who succumbed after the process had lasted for some years, but while the inflammatory process in the glomeruli was still active. The histology of the lesion is identical with that seen when an artery is ligated, and the opinion is advanced that the endarteritis obliterans is due to the glomerular lesion blocking the blood current.

3 Arteriosclerosis similar in histology and distribution of the lesions to that found in essential hypertension was present in all twelve cases of secondary contracted kidney. It was not found in early cases and was of but slight degree in the moderately advanced cases. The occurrence of arteriosclerosis is correlated with hypertension of long duration.

4 Muscular hypertrophy in the media of the renal arterioles was well marked in many cases of chronic glomerulonephritis of considerable duration but still "active." It was not found in the early stages. In cases of secondary contracted kidney of many years' duration the medial muscle usually atrophies as it does in essential hypertension.

5 The fact that arteriosclerosis of the same histology and distribution as that found in essential hypertension occurs in chronic glomerulonephritis of long duration is strong added evidence that this lesion is a consequence of the hypertension.

MULTIPLE MYELOMA

WITH REPORT OF A CASE *

THOMAS J CHARLTON, M D

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Multiple myeloma is a disease of the bone marrow characterized by the appearance of multiple focal lesions which exhibit certain neoplastic properties. The histologic picture is that of a proliferation of apparently some one cell of the marrow, but the histogenetic identity is still unsolved. Metastases have been reported but are rare. Bence-Jones protein in the urine is a frequent accompaniment. All cases reported have terminated fatally, usually after having run a slow, progressive course.

The first case of this disease reported was that of McIntire, in 1850, under the term *mollities ossium*. In 1867, Wever reported another case. Von Rustisky in 1873, first recognized the involvement of the bone marrow and gave it the name it now bears, multiple myeloma. In 1905, Wood was able to collect only thirty instances of this disease,¹ fifty had been collected in 1912, and a hundred by 1920. Since then the total has been raised to 140.² This rapid increase during the past few years is not believed to be due to an increase in incidence but to the advent of the roentgen ray which facilitates diagnosis, and without which in some cases the disease would not be recognized. Sixty per cent of the cases reported occurred in persons between 40 and 60 years of age, but the extreme ages recorded are 24 and 69 years.³ This disease occurs more commonly in men than it does in women: men, 76 per cent, women, 24 per cent. The reason for the predominance in men is not known.

The origin of the cells of multiple myeloma has been much discussed, and at present few authorities are in accord concerning their derivation. It is generally accepted that they arise from cells in the bone marrow, because it is here that the tumor is found. As the name implies, the foci of origin are multiple, and the distribution of the growth throughout the bones is widespread. Ewing,³ reviewing the work of other observers, classifies them into four types: (1) plasmacytoma, (2) erythroblastoma, (3) myelocytoma, adult and embryonal,

* From the Second Medical Division, New York Hospital, New York

1 Wood. Chemical and Microscopic Diagnosis, New York, D Appleton & Co., 1905

2 Newburn and Vango. Canad M A J **15** 502 (May) 1925

3 Ewing. Neoplastic Disease, ed 2, Philadelphia, W B Saunders Company, 1922, p 292

and (4) lymphocytoma. He thinks that each shows distinct types of cells and not varying phases of anaplasia. Vance⁴ says "While the clinical and pathological features of the cases of multiple myelomata are remarkably similar, a variety of types of multiple myeloma have been distinguished on the basis of the histological characteristics of the tumor cells. There is no doubt, however, that these cells, diverse as they are, are derivatives of the undifferentiated cell of the bone marrow or the myeloblast which is the ancestor of both leucocyte and erythrocyte." He supports this claim with the fact that cells of multiple myeloma almost always resemble certain elements of normal marrow.

Much work has been done in the attempt to prove whether these cells belong to the myelocytic series. Normal myelocytic cells should show granules, and many workers have attempted to demonstrate these granules in multiple myeloma. Beck and McCleary⁵ were able to show oxydase granules in the plasma cells in one case of plasmocytoma. Most other authorities have not been able to confirm this. McConnell⁶ believes that plasma cells are young myelocytes not mature enough to give the oxydase reaction.

Some consider these tumors in the light of an infectious process or granuloma because of the slow progress of the disease, and because the type of cell found in the plasma cell type at least, is seen in chronic infection. If this be true, one would expect the reaction to be a lymphocytic one. This agrees with the belief held by some writers that plasma cells are derived from lymphocytes. Kingsley, Unna and others⁷ support the infectious theory. They believe that plasma cells are derived "directly from connective tissue fibroblasts or indirectly from histogenous lymphoid cells which themselves are derived from fibroblasts." If it be assumed that the plasma cells in multiple myeloma are the same as those found normally and pathologically, then they are the result of a specific cell reaction. There is some evidence to prove that all multiple myelomas are derived from plasma cells of bone marrow origin. Mallory⁸ states

The cell type of this tumor has not been determined. Evidently it does not belong to the myeloblastic series because it does not differentiate like them. Moreover the myeloma is never associated with myelogenous leukemia. The only other cells peculiar to the bone marrow are the erythroblast and the megakaryocyte. Possibly it arises from one of these cells. It is claimed by some writers that there exists in the bone marrow another peculiar kind of cell which they call the bone marrow plasma cell, and that from it this tumor arises.

4 Vance. *Am J M Sc* **152** 693, 1916

5 Beck and McCleary. Multiple Myeloma with Bone Marrow Plasma Cells in the Blood, *J A M A* **72** 480 (Feb 15) 1919

6 McConnell. *Am J M Sc* **165** 184, 1923

7 Kingsley. *Anat Record* **29** 1 (Nov) 1924

8 Mallory. *Pathologic Histology*, Philadelphia, W B Saunders Company, 1914, p 338

Bailey⁹ states definitely that a plasma cell is found in normal bone marrow. In Christian's¹⁰ eight cases of multiple myeloma he found them all of plasma cell origin. He says, "The cases studied side by side and in comparison with bone marrow cells leave the impression that we have in these tumors a development from certain bone marrow cells which I have considered to be bone marrow plasma cells. Whether this be true for all reported cases is exceedingly difficult to say. Possibly some cases have to be considered as exceptions." Williams¹¹ points out that

Further research may show that the differences in the type are more apparent than real and are the result of differences in fixation, staining, and description or perhaps in degree of anaplasia. The problem is further complicated by the fact that the exact microscopic characters of the plasma cells are keenly disputed, while their occurrence in normal bone is not universally recognized.

Gross pathologic examination shows areas of soft or firm tumor tissue scattered throughout the marrow of the bones. Those most commonly involved are the flat bones, the sternum and the ribs, in which blood formation is most active. These areas vary in color from gray to red, depending on the amount of blood in them. The masses of tumor tissue may be small and discrete or large and confluent. The tumor appears to rise from multiple foci, and the involvement is usually widespread. It is by pressure on the surrounding bone that the tumor causes absorption, and this explains its ragged appearance in the roentgenograms. The tumor cells in themselves have no real bone destroying property, nor have they the power to form new bone. In this respect they differ from the cells of osteogenic sarcoma. Sometimes the tumor breaks through the periosteum and invades the surrounding tissue, giving the bone a nodular appearance.

Bence-Jones protein is found in the urine in about 80 per cent of the cases of multiple myeloma, and it is by this finding that many instances are first recognized. It is not pathognomonic of the disease, for it is occasionally present in other pathologic conditions of the bone or marrow, such as lymphosarcoma, osteomalacia, leukemia, myxedema and carcinomatous metastases. This protein was first described by Bence-Jones in 1847, who considered his case as one of *mollities ossium rubra*. At first this substance was thought to be more of the nature of an albumose, but now it is held to be a true protein, yielding characteristic amino-acids on hydrolysis.¹² The origin of Bence-Jones protein is not known. Characteristic lesions are not seen in the kidneys

⁹ Bailey. Textbook of Histology, ed. 6, New York, William Wood & Co., 1920, p. 199.

¹⁰ Christian. J. Exper. Med. **9** 325, 1907.

¹¹ Williams, O. T., and others. Lancet **2** 1403, 1910.

¹² Boggs and Guthrie. Am. J. M. Sc. **144** 803, 1912.

either grossly or microscopically. Some of the theories are that it is due to (1) rapid destruction of bone by neoplasm, (2) the action of an enzyme of the tumor cells on the proteins in the blood, (3) a peculiar secretion or degeneration product of the myeloma cells. The characteristic feature of this protein is that when its solution is heated in an acid medium at as low a temperature as 45 C, a turbidity is noted. At from 50 to 55 C a flocculent precipitate forms which adheres to the side of the tube. Above 60 C the precipitate begins to disappear and on boiling completely disappears. When the solution is cooled, it reappears. The reaction is often concealed somewhat by the simultaneous presence of serum albumin. Bence-Jones protein may occur in a specimen of urine constantly or intermittently. In some cases the protein has been known to be precipitated spontaneously shortly after being passed. Bayne-Jones and Wilson¹³ found that there were differences between Bence-Jones protein and the proteins of human serums and also between preparations of Bence-Jones protein from various sources. Their specimens of Bence-Jones protein were all the same regarding their phases of coagulation and solution by heat in an acid medium, yet their physical properties differed much, as did their immunologic reactions. These differences were so marked that they regarded the so-called "Bence-Jones body" as a group of similar but not identical substances, and referred to the group as the Bence-Jones proteins. This immunologic difference was confirmed by studies made in the New York Hospital.

The blood picture is usually that of a progressive secondary anemia. The white cells range from five to fifteen thousand. Abnormal cells have seldom been reported. In a case described by Beck and McCleary¹⁴ a blood smear showed 66 per cent plasma cells, and later at autopsy the same type of cell was found in the tumor. In a case reported by Ellermann¹⁴ the blood picture was that of a leukemia. There were many nucleated erythrocytes in a case reported by Jochman and Schumm¹⁵. At times, anemia is the dominating feature, and it resembles that of the pernicious type in a few cases. In the case that is reported in this article there are some points that seem to indicate that the anemia is due to an increased destruction of erythrocytes, namely, an icteric index of 10.6, and the hemosiderosis in the liver and spleen. These conditions do not occur in a simple anemia.

The blood in these cases is, as a rule, not associated with a diminished calcium content but with a rather high one. Blatherwick¹⁶ found in

13 Bayne-Jones and Wilson. *Bull Johns Hopkins Hosp* **33** 37 (Feb.) 1922

14 Ellermann v. Myelomas with Leukemic Blood Picture, *Ugeskr f Laeger* **85** 501 (July 19) 1923

15 Jochman and Schumm. *Ztschr f klin Med*, vol 46, 1902

16 Blatherwick. *Am J M Sc* **151** 432, 1916

his case that the analysis of the feces and urine showed an abnormally high excretion of calcium. In the case which is being reported the patient was able to produce a considerable callus formation around her fractures, and at autopsy a part of the aorta showed marked calcification. Microscopically areas of calcification were found also in the kidneys. In his case McConnell⁶ reports the presence of calcification in the heart, lungs, kidneys, spleen and pancreas. He explains this as a result of the growth of the tumor with the resulting destruction of bone which causes a large amount of calcium to be liberated. The calcium is carried in the circulation and deposited in the different organs, particularly in the walls of vessels.

The onset of this disease is usually insidious and has progressed extensively before it is recognized. There are several ways by which attention is first attracted to it, namely (1) pain of a dull, boring nature which is frequently made worse by pressure, (2) a pathologic fracture, when this occurs in the vertebrae, a marked kyphosis may result, (3) paraplegia or a neurologic disturbance most frequently of the lower extremities, which results from destruction of the vertebrae with pressure on the cord or spinal nerves, and (4) accidental finding of Bence-Jones protein in the urine during a routine urinalysis. Probably the commonest early symptom is the dull boring pain over the chest and back, which seems to be due to pressure of the tumor on the periosteum. When the cranium is involved, headache is a symptom. Pain in various organs and in the intestines has been described, the pain being of a referred nature and due to pressure on the spinal nerves. A progressive anemia is one of the most striking features of this disease, and it is associated with more or less cachexia. Fever may or may not be present and is never extremely marked. Metastases rarely occur in the organs, and if they do occur, they are not likely to give rise to symptoms. In some cases the spleen is enlarged, but this is not a common observation, the spleen usually being of normal size. There is an increasing loss of weight and a general progressive weakness, so that finally the patient becomes bedridden. The course of the disease varies much. Some fulminating cases terminate in a few months, while others pursue a slow course over many years. Remissions may occur, but there is not a case on record in which the disease has been stopped or even checked. Intercurrent infections frequently are fatal before the disease has run its course.

The differential diagnosis, especially in the early stages of the disease, is not easy. The condition may simulate pernicious anemia particularly when cord symptoms are present. From pressure on the spinal nerves sharp pains in the thighs arise which make one think of tabes dorsalis. Pott's disease is hard to eliminate when the vertebral column is eroded and the cord compressed. Pathologic fractures may occur with sarcoma

of bone or metastatic carcinoma, so they are not pathognomonic. Gastro-intestinal carcinoma must be considered on account of the cachexia, general weakness and loss of weight. The pain over the chest is not much different from that caused by eroding aneurysms. Osteomalacia is the condition hardest to differentiate, and it was with this disease that multiple myeloma was first confused. They both may give the same blood picture and both show Bence-Jones protein in the urine. The clinical course is often similar. However, osteomalacia occurs more commonly in women, while multiple myeloma is more frequently found in men. The roentgen-ray observations in both conditions are definite and serve to differentiate them. Most of these confusing conditions can be ruled out by finding Bence-Jones protein in the urine, by the blood picture and by the symptoms and general clinical condition of the patient, but the diagnosis can be made definitely only by aid of the roentgen ray or by biopsy. The roentgen-ray observations are characteristic, the bone showing numerous small discrete areas of rarefaction with a ragged moth-eaten outline. This is due to pressure of the nodules which causes an irregular absorption of the bone. As a rule, the cortex is not destroyed.

The treatment of this disease, like that of most other malignant tumors, is not satisfactory. In none of the cases reported has the growth been checked or stopped. Roentgen-ray therapy and the Alpine lamp seem to ameliorate the symptoms. Iron and arsenic such as are used in secondary anemia usually do not give striking results. Much care has to be taken in the nursing of these patients because of the ease with which pathologic fractures occur.

REPORT OF CASE

History—The patient was a German woman, aged 57, who had lived in this country since she was 18 years old. Her occupation had been packing tobacco. She was married for many years but had not had any children. She had enjoyed perfect health until five months before being admitted to the hospital. Her family history was negative. Five months before admission the patient had had a sudden attack of pain in the lumbar region. This pain became constant, and the patient was told she had lumbago. Her back was strapped, and in the course of six weeks the pain gradually disappeared. Later while lifting a heavy load she felt a sudden sharp twisting pain in the right hip. This pain occurred at intervals for about two weeks and then stopped. Shortly afterward she had a similar attack of pain in the left hip. Since then, pain had been almost constant. When the patient was admitted to the hospital, the pain was in the lower part of the back and left side and caused her to bend backward when walking. The pain was relieved by lying down. In the previous five months she had lost about 50 pounds (22.7 Kg.), her weight on admission having been about 145 pounds (65.8 Kg.). Her appetite was good, and she slept well. Except for the pain described, the patient felt well. She consulted a physician who in the course of his examination found Bence-Jones protein in her urine. He advised hospital treatment, and she was admitted to the service of Dr. William R. Williams at the New York Hospital on Dec. 5, 1922.

Physical Examination—The physical examination at this time was essentially negative. It was not until sixteen months later, at the time of her last admission, that any physical defects were noted. At that time it was seen that the patient was extremely weak, but there were no gross changes except those in her extremities. The left thigh showed a partial loss of motility, and there was entire loss of motility of the right thigh at the hip joint. There was some shortening and irregularity of outline of the right femur in its upper third.

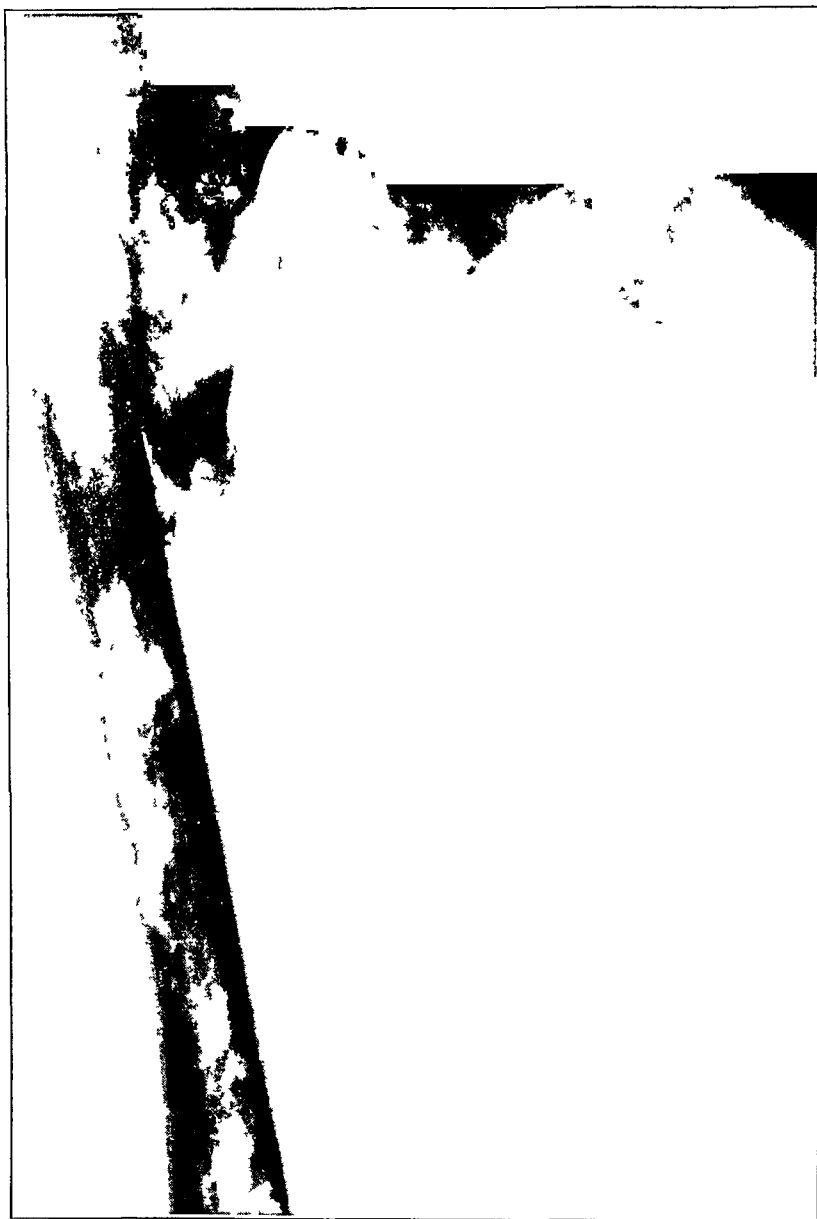


Fig 1—Involvement by multiple myeloma of pelvis and right femur, with pathologic fracture of femur

This patient was under observation intermittently from December, 1922, to September, 1925, and spent the last seventeen months of her life in the hospital. Until three months before her last admission the patient was able to be up and around. At that time she fell and sustained a fracture of the left hip. Her condition became gradually worse, so that hospitalization became necessary.

Bence-Jones protein was found in the urine shortly before the patient first came under observation in 1922, and it was present in all subsequent examinations, the amount varying from a faint trace to a heavy precipitate. Serum albumin was also present, the amount changing from time to time, and occasionally being so great as to obscure the Bence-Jones reaction. Hyaline and granular casts were found at irregular periods. A few epithelial cells, leukocytes, and occasionally calcium oxalate and phosphate crystals were recorded. The urine was usually acid, and the specific gravity ranged from 1,012 to 1,030, the average being around 1,020.

The blood count on first admission showed a hemoglobin content of 60 per cent, leukocytes 7,600, erythrocytes 2,260,000 and a normal differential count. Throughout her stay in the hospital, the blood count remained practically the same except



Fig 2—Rarefaction in left clavicle, scapula, humerus and ribs

for a gradual diminution of the hemoglobin. The last examination shortly before death showed hemoglobin 22 per cent, erythrocytes 2,200,000 and leukocytes 4,700. Smears at different times revealed some poikilocytosis and slight anisocytosis, but in general the red cells appeared normal. At no time were more than a few normoblasts seen, and the platelets appeared normal in number. No abnormal white cells were noted.

Several blood Wassermann tests performed at various times were negative. Chemical examination of the blood showed a variation in the urea nitrogen from 11.5 to 23 mg per hundred cubic centimeters of blood. The blood calcium ranged from 12.06 to 16 mg per hundred cubic centimeters of blood. The icteric index, which was determined only once, was 10.6.

Roentgenograms taken in December, 1922, showed rarefaction of ribs, clavicles, vertebrae and extensive lesions in the skull. However, of the long bones, only

the fibulae and bones of the forearms were involved. Three months later, the lesions noted before were more extensive, and, in addition, rarefaction was beginning in the tibiae and femurs. Roentgenograms taken two months later revealed further advancement of the disease. When roentgen rays were next taken, in March, 1925, three pathologic fractures of the femurs were noted. The patient was aware of only one of these, which she had experienced several months previously. While being taken to the roentgen-ray room for therapy, another fracture occurred in the left femur. Fractures were also noted in the right clavicle and later in the right forearm. Roentgenograms taken of the chest showed that practically all the ribs on the left side were broken, these having given rise to no symptoms. Shortly before death pathologic fractures of both bones of the forearm and of the lower end of the humerus on the left side were noticed.

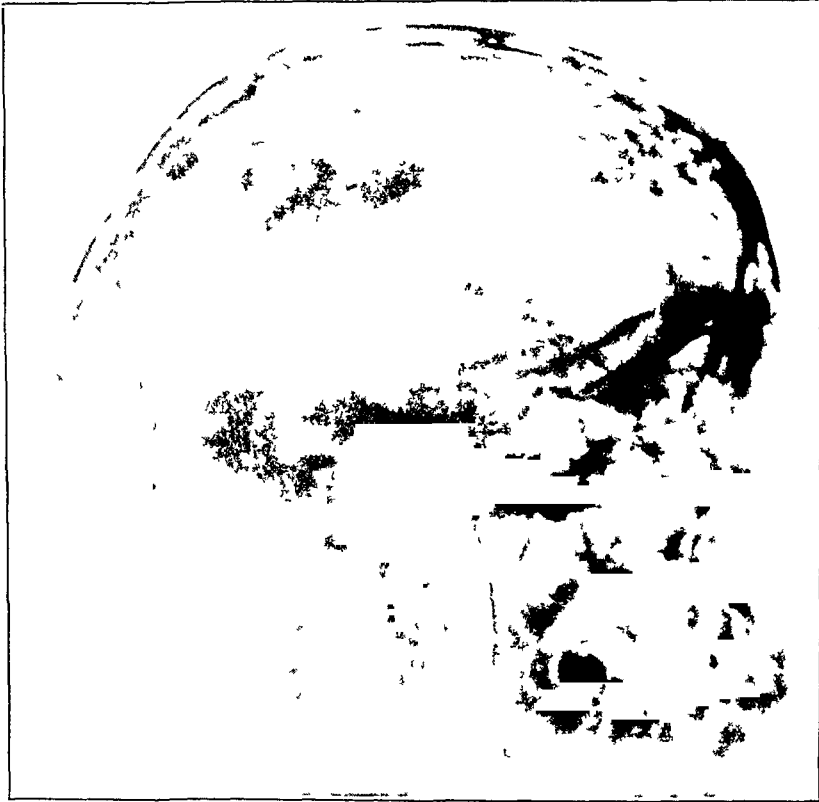


Fig 3—Extensive lesions in the skull

Treatment and Course—When first admitted to the hospital the patient was given extensive roentgen-ray therapy all over the body, but this had to be discontinued on account of pathologic fractures, and the Alpine lamp was substituted. As a result of these procedures there seemed to be an amelioration of symptoms. Sodium cacodylate was given daily for several months without any apparent effect on the blood.

Throughout the patient's last stay in the hospital, which was about seventeen months, her clinical course was variable but generally downward. At times pain over the chest and back was severe enough to require morphine, but in general the patient was comfortable as long as she remained quiet. She gradually became weaker, and for several weeks before death had frequent vomiting and diarrhea. The weakness became extreme, and the patient finally succumbed. During the last few weeks there was a slight irregular fever, but aside from that the temperature was normal.

Pathologic Report—Autopsy was performed shortly after death. The loose folds of the skin indicated considerable loss of weight. The left upper arm was deformed, and by palpation a fracture was noted at about the middle of the humerus. Both femurs showed deformities.

At numerous places of the skull areas of extremely thin bone were encountered. The slightest pressure on these areas caused an indentation of the bone attended by a crackling sound. On section, the external table showed irregular erosion, and the internal table consisted only of a flat network of thin bone. The diploe was replaced by soft yellowish masses of tissue which extended through meshes of the internal table and were connected with the dura from which it could not be separated. Only slight pressure was sufficient to cause a fracture of the sternum, and the bone was easily cut. The cut surfaces showed the bone to be thin, in some places only 2 mm in thickness. The medullary cavity was filled



Fig 4—Skull showing lacelike destruction of inner table. Tumor can be seen between inner and outer tables.

with masses similar to those found in the skull, and, in addition, definite nodules of light red were found within the yellow masses. The lower end of the right femur was removed. On vertical section the marrow appeared replaced by reddish masses of soft tissue with a great many hemorrhages scattered through it. The epiphysis of the femur did not reveal gross lesions. The observations on the ribs and vertebrae were the same as those described in the foregoing.

The spleen was of normal size and consistency. On section, the organ presented a brownish surface with many scattered hemorrhagic areas, normal markings could not be recognized.

The liver, which weighed 1,200 Gm, was yellowish brown and showed gross evidence of fat infiltration, otherwise it was normal.

The surfaces of both kidneys appeared roughly granular, and a few larger scars were present, otherwise the organs appeared normal.

Adenopathy was not present in the lymph nodes. The largest nodes encountered were about 1 cm in diameter. A few nodes appeared anthracotic, but other gross lesions were not apparent.

The abdominal aorta presented several large arteriosclerotic ulcers, in places calcification was so advanced as to cause the vessel to be rigid. This same lesion was present in the first portion of both coronary arteries. No lesions were noted elsewhere.

The fat of the subcutaneous tissue had a peculiar golden yellow color resembling that seen in pernicious anemia.

Aerobic and anaerobic cultures of blood from the heart showed no growth.

Microscopic Examination—On section the spleen showed a marked hyperemia and numerous accumulations of brown pigment granules. There were also many cells loaded with such granules. The walls of some of the capillary vessels showed thickening with hyalinization.

In the liver cells of the peripheral parts of the lobules were numerous large, round, empty vacuoles, evidently the result of fat infiltration. Most of the capillary blood vessels contained many large cells with acidophilic protoplasm. The large

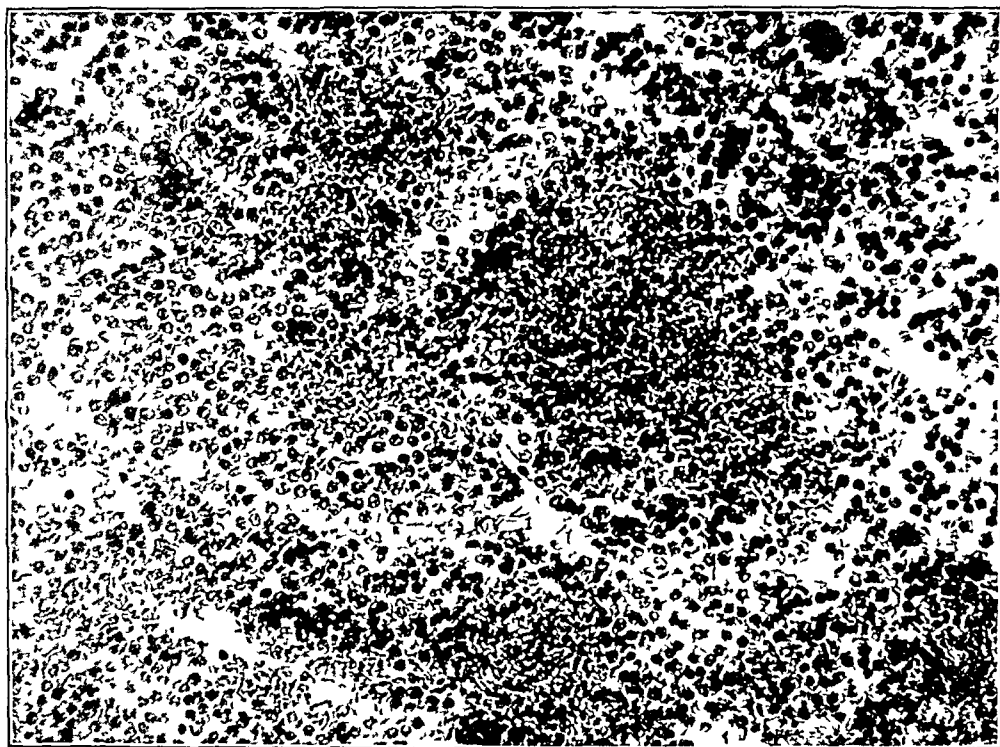


Fig 5—Growth in bone marrow showing plasma cells

vesicular nucleus was rich in chromatin, and the structure of the latter was often radiating. The nucleus of most of these cells was eccentrically placed. These cells resembled plasma cells.

In the kidney the majority of the glomeruli were intact, but there were scattered areas in which the glomeruli were in various stages of hyaline degeneration. Throughout the specimen there was a definite increase of interstitial fibrous connective tissue with a patchy mononuclear round cell infiltration. A large proportion of the tubular lumina was filled with a homogenous or granular material which varied in color from pink to pale blue. In a few instances the tubular epithelium was replaced by a deep blue staining structure, this process undoubtedly being calcification.

A section of the tumor mass taken from the right femur, presented a uniform histologic picture. Here were seen a great many identical cells closely packed together. These cells were similar to those described in the liver capillaries and resembled plasma cells. In the adjacent fatty bone marrow, groups of similar

cells were encountered. Sections of the tumor mass taken from the skull and vertebra showed the same cells.

Summary—The conditions revealed at autopsy were plasmocytoma of the bone marrow, hemosiderosis of the spleen and liver, glomerulonephritis, chronic, 'calcium metastases' to the kidneys and pathologic fractures.

Note—I have classified this tumor as a plasmocytoma, signifying that the cellular units of which the growth consisted, resembled plasma cells, implying, however, nothing concerning their histogenesis or real nature.

SUMMARY

A case report of multiple myeloma occurring in a woman, the patient being under observation for over two and one-half years is given in the foregoing. Attention was first directed to the condition by a pain in the back, made worse by pressure. Bence-Jones protein was found in the urine, and on the basis of these two conditions a provisional diagnosis of multiple myeloma was made, roentgen-ray observations confirmed the diagnosis. The blood picture was that of marked secondary anemia. The icteric index and hemosiderosis of the liver and spleen at autopsy suggested that the anemia to a certain extent may have been of a hemolytic nature. The course of the disease was marked by progressive anemia and many pathologic fractures. At autopsy several pathologic fractures were seen, and most of the bones were destroyed by the tumor growth of the marrow. The histologic structure of the tumor tissue was that of a plasmocytoma. No metastases were found but plasma cells were present in the capillaries of the liver.

AUDIBILITY OF BRUIT OF THE THYROID IN EXOPHTHALMIC GOITER

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The typical thyroid swelling in exophthalmic goiter presents throbbing, thrill, and bruit—physical signs of hyperplasia of the organ associated with a tremendous increase in its vascularity. These signs, especially bruit, help to differentiate this form of goiter from that of toxic adenoma. Indeed, in the absence of exophthalmos in an otherwise typical case of exophthalmic goiter, the characteristic bruit of the thyroid is almost pathognomonic. The stethoscope over the thyroid gland is frequently the determining factor in differentiation of the two conditions, which otherwise present many clinical features in common.

The examiner must place the stethoscope over the isthmus of the organ rather than over the lateral lobes. At the isthmus the true bruit of the thyroid is obtained rather than the sound of blood passing through the carotid arteries. Carotid murmurs are systolic in time, of the same duration as the cardiac systole and rather soft in character. Bruit over the hyperplastic thyroid is likewise systolic in time but of greater duration than is the cardiac systole, occasionally it is also diastolic. In typical instances the sound heard is rather loud and at times uncomfortably harsh to the ear, simulating the bruit heard over an aneurysm.

In a considerable percentage of sufferers from exophthalmic goiter there is no obvious thyroid swelling, hence bruit is scarcely to be expected. Again, during the formative or incipient stage of the disease, thyroid vascularity may be insufficient to produce an undoubted murmur. In cases of otherwise typical exophthalmic goiter, hyperplasia may be added to an adenoma of the thyroid of long standing, hence bruit may or may not be audible.

There are two methods of altering the audibility of bruit in the hyperplastic thyroid of exophthalmic goiter: (1) through change of the patient's posture, and (2) through the use of iodine.

1. The usual position of the head during examination of the thyroid is one of extension, with the chin raised upward and the anterior aspect of the neck made taut and convex as in figure 1. In this position the examiner determines the motility of the organ during deglutition, the size, shape and symmetry of the mass and the location of the lower border of the isthmus, to determine whether there is any retrosternal extension. The stethoscope over the isthmus with the patient's thyroid in this position will, however, give the least likelihood of bruit, as the blood vessels are compressed, and the organ is made relatively anemic. In marked hyperplasia of the thyroid this compression will suffice merely

to render bruit less audible. Questionable bruit or bruit of moderate loudness will become entirely inaudible. When, however, the patient's neck is placed in the flexed position with the chin forward or approaching the chest, as in figure 2, a soft bruit becomes loud, a questionable one rather distinct, and often a thyroid presenting no bruit in the extended position will present one in this posture. I have by this means produced a decompression or release of tension of thyroid content so that the maximum of vascularity exists with consequent maximum



Fig 1—Extended position of the head during examination of the thyroid



Fig 2—Flexed position of the head during examination of the thyroid

audibility of bruit. It is frequently possible in this position of the neck to elicit bruit over the thyroid months in advance of the development of marked enlargement of this organ in exophthalmic goiter, thus assisting in the making of an early diagnosis.

2. As the result of the administration of iodine in patients with the hyperplastic thyroid of exophthalmic goiter, there is such an accumulation of colloid within the vesicles as to increase the size and tenseness of the goiter. This may cause such compression of the distended blood vessels within the thyroid as to render less audible or, virtually, to eliminate bruit. Discontinuance of iodine administration results in the disappearance of the excessive colloid accumulation within from ten to twenty days, with the reappearance of the former bruit.

PAROXYSMAL CYANOSIS

ASSOCIATED WITH BILATERAL THROMBOSIS OF THE SUPRARENAL
VEINS *

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AND

J A CAPPS, M D
CHICAGO

Bilateral thrombosis of the supra renal veins as a cause of death is rare, and the clinical symptoms caused are so puzzling that the diagnosis is doubtful until a postmortem examination demonstrates the lesions. Sudden destruction of both supra renal glands by extensive hemorrhages leads promptly to death¹ while a more chronic process, such as tuberculosis, brings about the changes of Addison's disease. Between these extremes are gradations of destruction and corresponding diminution of function which according to statements recorded may arouse a considerable variety of symptoms. These symptoms with acute injury of the supra renal gland have been arranged by Lavenson² and others in five groups: (1) a "peritoneal" form with epigastric pain, vomiting, at times diarrhea and profound prostration—symptoms resembling those in acute hemorrhagic pancreatitis, (2) an asthenic form ending fatally in a few days, (3) a nervous type with convulsions, delirium or coma, (4) a form with purpuric rash or hemorrhages in the abdominal viscera occurring especially in children and (5) finally a variety in which death is sudden and which is usually seen in children and in stillborn infants. Symptoms aroused by the sudden loss of supra renal function, which lead at least to a presumptive clinical diagnosis of injury to the supra renal gland, are complicated by symptoms resulting from fluctuations in the suppression of function, which occur with partial thrombosis of the veins, organization of the thrombi and further occlusion of the vessel lumens. Very little regarding the symptoms of this disorder is mentioned in the reports now on record and judging from the statements made in these accounts thrombosis of the supra renal veins was considered secondary in importance. In 1885 Hanau³ reported thrombosis of the supra renal veins in three patients, two of whom had acute suppurative infections elsewhere in the body, the third had advanced

* From the Henry Baird Favill Laboratory, St Luke's Hospital

† Read by title at the Annual Meeting of the American Society for Clinical Investigation, Atlantic City, N. J. May 2, 1927

1 Crowe S. M., Tr. Chicago Path. Soc. **12** 26 (March) 1924

2 Lavenson R. S., Acute Insufficiency of the Suprarenals Arch. Int. Med. **2** 62 (Aug.) 1908

3 Hanau. Tageblatt der Vers. deutscher Naturforscher und Aerzte, Strassburg 1885 p. 229

pulmonary tuberculosis. Thrombosis of the veins with extensive hemorrhage into the substance of the suprarenals is reported in three patients by Lissauer.⁴ He mentions bilateral thrombosis of the supra renal veins without hemorrhages in a patient with aortic stenosis. These, he thinks, are due to cardiac deficiency and resultant stagnation thrombosis. Simmonds⁵ reports the cases of seven patients, in three of whom both supra renal veins were thrombosed. He was unable to find bacteria in the thrombi, and regarded them as marantic. In an analysis of the clinical symptoms in seventy-nine patients dying with hemorrhages of the supra renal glands, Arnaud⁶ mentions unilateral thrombosis of the veins in two. Forty-four of these seventy-nine patients were without appreciable symptoms. The hemorrhage was of such volume in five as to give rise to an appreciable tumor. Symptoms of peritonitis occurred in six, supra renal insufficiency in nine and the apoplectic form accompanied by delirium, convulsions, coma or syncope occurred in fifteen. Bilateral thrombosis of the supra renal veins is given by Straub⁷ as the cause of an acute Addison's disease. The patient lived seventeen days. A carcinoma of the pylorus with metastases in the supra renal glands and complete occlusion of the supra renal veins were found after death. In 1922, Veit⁸ reported a case of acute Addison's disease in a woman, in whose body the postmortem examination demonstrated aplasia of the left supra renal gland and an organizing thrombus of the right supra renal vein. Thrombosis of the right supra renal vein with intarction of the gland and beginning thrombosis of the left vein in a woman with puerperal infection is recorded by Weissenfeld.⁹ He regards circulatory disturbances as the cause. A report of bilateral thrombosis of the supra renal veins in two more patients is made by Schonig.¹⁰ One of these patients was a woman with Staphylococcic septicemia following abortion, the other, a woman who died fifteen days after a ventrifixation of the uterus. The postmortem examination demonstrated small abscesses in the pelvic tissues and in the wound from the laparotomy. Cultures taken from the spleen showed staphylococcus.

The histologic changes occurring in the supra renal gland tissue with venous thrombosis may be relatively insignificant (Veit, Schonig, Lissauer). There are small regions of necrosis in the different layers of the cortex and medulla, and the amount of tissue destroyed may seem

4 Lissauer, Max. Virchows Arch f Path Anat **193** 137 1908

5 Simmonds, M. Virchows Arch f Path Anat **170** 242 1902

6 Arnaud, F. Arch gen de med **186** 5, 1900

7 Straub. Acuter Morbus Addisonii nach Thrombose beider Nebennieren Vene, Inaug Dis., Tübingen, 1909

8 Veit, Bernhard. Virchows Arch f Path Anat **238** 269, 1922

9 Weissenfeld, Felix. Beitr z Path Anat u z Allg Pathol **70** 516, 1922

10 Schonig, A. Beitr z Path Anat u z Allg Pathol **72** 580 1924, Centralbl f allg Pathol u Path Anat **36** 416, 1925

relatively small. In most of the reports thrombosis of the suprarenal veins was associated with other visceral disorders of so grave a nature that the clinical symptoms were difficult to interpret. Cyanosis was a conspicuous symptom only in the two cases reported by Clowe. In none of the cases reported was there paroxysmal cyanosis such as that in the patient whose clinical history is given in this article. Bittorf¹¹ recently described the clinical symptoms in a woman with thrombosis of the suprarenal vein which occurred because of a progressive ascending occlusion of the inferior vena cava, he refers to a similar observation recorded by him in 1910. After mentioning the symptoms caused in the patient (a middle-aged woman) by occlusion of the lower portion of the inferior vena cava, he says that the pulse, which had been of normal quality and tension, became faint and weak, finally being almost imperceptible, and that the skin of the entire body contained cyanotic spots resembling postmortem lividity. Respirations were deep and diminished to only a few per minute, they were not periodic. There was extreme weakness, and the temperature became subnormal. At first the sensorium remained clear, but after several days death occurred in coma. Bittorf thinks that some of these symptoms, if not all, resulted from a diminution of the supply of epinephrine. In another recent account of insufficiency of the suprarenal gland Medlar¹² records the clinical symptoms of a man, aged 28, whose entire illness was of about thirteen days' duration. Extreme cyanosis occurred, with other symptoms and the post-mortem examination demonstrated a marked atrophy of the cortex of the suprarenal glands and fibrous changes of the cortex and medulla.

REPORT OF A CASE

HISTORY—O. R., a white man, aged 30, entered St. Luke's Hospital on Jan. 22, 1926, complaining of weakness, shortness of breath, nervousness, sleeplessness, fulness of the head and headache, poor appetite and, finally, attacks of cyanosis.

Just before Jan. 1, 1926, he had contracted a stubborn cold and had made his condition worse by taking part in several drinking parties after which he awoke in the morning with headache and puffiness of the face. Soon after this, his mother noticed that while asleep his face and lips were purple, though breathing was normal. This cyanosis so alarmed the mother that she made nightly observations, always she noted the same blueness while the patient was asleep, but it disappeared after he arose in the morning. Later, he was aroused from sleep with some difficulty. He continued at his daily work until January 14. At that time, swelling of the ankles was present in the morning, but disappeared with exercise, afterward continuing during the twenty-four hours. Sleep was disturbed by the cyanosis, and breathing became labored. Later he complained of fulness in the head and ears, dizziness and nausea sometimes accompanied by vomiting.

In early life he had had pneumonia, measles and tonsilitis, but no rheumatism or heart trouble. Following a fall at the age of 2 he had a spinal deformity, and at the age of 12 he had a discharging sinus over the clavicle, this condition was diagnosed as tuberculosis of the spine. In spite of the deformity, he exercised vigorously, and never suffered from cyanosis or dyspnea. He used tobacco

11 Bittorf, A. *Munchen med. Wchnschr.* **73** 1928, 1926.

12 Medlar, E. M. *Am. J. Path.* **3** 135, 1927.

moderately, and alcohol occasionally, though seldom to excess. He said that he had not had venereal diseases, and the family history did not mention tuberculosis or epilepsy.

Physical Examination—The patient was a young man, apparently not acutely ill, with slightly blue lips, respirations 20, pulse rate 110 and temperature 99 F. The pupillary and other reflexes were normal. The thyroid and cervical lymph glands were not enlarged. He had a marked kyphosis of the cervical dorsal spine and an old scar on the right side of the neck. The lungs were clear, except for an occasional moist râle at the bases. He had enlarged liver, a slight ascites and a moderate swelling of the feet. The heart was moderately enlarged. The heart beat was rapid and regular, but without murmurs. The blood pressure was 126 systolic and 60 diastolic. Examination of the blood revealed hemoglobin, 86 per cent, red blood cells, 5,070,000, leukocytes, 18,000 per cubic millimeter with an increase of the polymorphonuclear cells. The Wassermann test of the blood was negative. A trace of albumin and a few red blood cells were found in the urine, but no sugar. A roentgen-ray examination demonstrated the spinal curvature, a moderately dilated heart and a normal aorta. A tentative but not altogether satisfying diagnosis of cardiac decompensation was made.

Course and Treatment—During the patient's stay in the hospital his symptoms resembled those in cardiac decompensation. The skin was slightly blue, the respirations were about 22 per minute and the blood pressure ranged from 120 to 140 systolic and from 70 to 75 diastolic. Several times during the day and night he suddenly became nervous, the color of his face changed to a deep purple as if he were being strangled. The cyanosis spread to the arms, trunk and legs, and breathing was labored. He often became unconscious during these attacks and the pulse rate was thready or imperceptible. With stimulation by caffeine, digitalis, oxygen or epinephrine, he regained consciousness in a few minutes, and his pulse, respiration and color became normal, but he was exhausted.

Preceding and during these attacks there was no bronchospasm or cardiac pain. Anorexia, nausea and at times vomiting occurred. The bowels were distended, and the movements were watery. Pigmentation of the skin or mucous membranes was not observed.

The paroxysms of cyanosis, dyspnea and unconsciousness grew more severe until February 10, nineteen days after admission and about six weeks after the onset of symptoms, when the patient passed into convulsions and died.

Postmortem Examination—The tissue changes found at postmortem examination of the trunk, head and neck, with the exception of a moderate passive hyperemia of the viscera generally, were confined to the suprarenal glands. The brain was fixed in liquor formaldehyde. In the thin frontal sections through the cerebrum and cerebellum, and in the transverse sections of the brain stem there were no gross changes or hemorrhages. A histologic examination of the brain was not made. A firm, but friable, gray thrombus, 0.6 cm. in diameter, projected into the inferior vena cava from the mouth of the right suprarenal vein. The lumen throughout the vein was completely filled with this mass. The suprarenal gland weighed 7.4 Gm. The left suprarenal gland weighed 6 Gm., and the vein also was filled with a firm, gray thrombus. These suprarenal glands were not enlarged, the medullary portions were a dark reddish brown, and the yellow lipid substance of the cortices was diminished and irregularly distributed.

Histology—In sections taken through the middle of the right suprarenal gland, including the vein, three-fourths of the lumen was filled with a mural thrombus in which were small capillaries and other changes occurring with the organization of a fibrin mass. The remaining portion of the lumen contained masses of red blood cells and a few polymorphonuclear leukocytes (figs 1 and 2). The cytoplasm of most of the cells in the medulla was shrunken to about one-third of the original size, and the nuclei were pyknotic. The spaces left by the shrunken cells appeared as vacuoles. The amount of fibrous stroma was unchanged. The cells of the zona glomerulosa did not stain uniformly. Some portions contained cells quite normal in appearance, but adjacent to these were

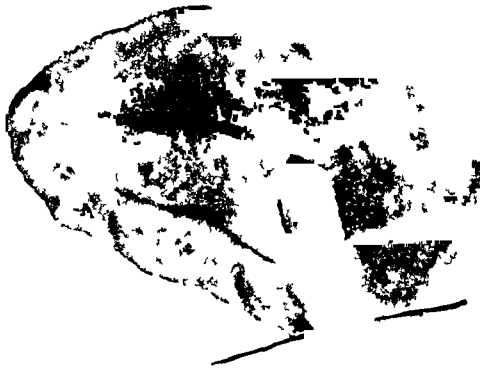


Fig 1—Sketch illustrating the thrombus in the right suprarenal vein



Fig 2—Photomicrograph of the thrombus in the right suprarenal vein, $\times 50$

other portions with only granular, necrotic cellular substance. The cells of the zona fasciculata were markedly vacuolated, some with shrunken nuclei and others with vesicular nuclei, and a few were necrotic. Similar changes were present in the zona reticularis. The hemorrhages present were relatively small and did not involve any large part of the tissues.

The changes in the left suprarenal gland were like those of the right, excepting that the changes in the cells were less extensive. The thrombus in the vein was recent. The central portion of the thrombus consisted of a dense mass of polymorphonuclear leukocytes, and the peripheral portions were fibrin lamellae with a few polymorphonuclear leukocytes and masses of red blood cells (figs. 3 and 4). In preparations stained in methylene blue, structures resembling cocci were found in pairs and in chains of as many as four.

COMMENT

Chronic suprarenal insufficiency in Addison's disease is characterized by an insidious onset, pigmentation of the skin, gastro-intestinal symptoms, low blood pressure and finally by progressive asthenia. The disease terminates by gradual exhaustion, by syncope or by the development of delirium with dyspnea, except when the tuberculous infection is widespread.

Acute and subacute suprarenal insufficiency is rarely recognized clinically. The acute forms in patients are mistaken for peritonitis or pancreatitis or are not diagnosed. The subacute form enables a longer period of study and observation, but unfortunately most of these cases occur in patients with some infection or suppurative process that obscures the disorder in the suprarenal glands. In the acute and subacute insufficiencies, pigmentation of the skin does not occur, but other symptoms, such as asthenia, arterial hypotension, gastro-intestinal disorders and cerebral disturbances, are usually manifest and should at least suggest the possibility of a suprarenal lesion.

The clinical history reported in this article is unusual in that the postmortem examination of the body of the patient demonstrated no changes other than in the suprarenal glands, nor was there any lesion of the aorta or coronary arteries to explain the progressive decompensation of the heart. The initial cold was an infection of so mild a nature that without some further complication death was not explained clinically. The clinical symptoms also suggest some disturbance other than a simple decompensation of the heart. It is true that attacks of dyspnea and cyanosis occur in cardiac disease, particularly in aortitis and in disease of the coronary arteries, with or without pain. But in this patient attacks of cyanosis appeared before the dyspnea. Later, these severe attacks of cyanosis were accompanied by a rapid fall in arterial pressure and unconsciousness. These symptoms are especially noteworthy because changes of the aorta and coronary arteries were not found in the postmortem examination. Bronchospasm may cause cyanosis and dyspnea but the breathing characteristic of this disorder was not present during the attacks.



Fig 3—Sketch illustrating the thrombus in the left suprarenal vein



Fig 4—Photomicrograph of the thrombus in the left suprarenal vein, $\times 50$

In discussing mixed thrombi of the suprarenal veins Dietrich and Siegmund¹³ say that these are propagating thrombi whose origin is in the capillary bed. They arise because of retrogressive changes of the suprarenal substance especially those caused by bacteria. It seems likely that the thrombosis of the suprarenal veins in this patient occurred as a complication of the respiratory infection and that the subsequent attacks of cyanosis, syncope, nausea and weakness and the cardiac weakness resulted from insufficiency of the suprarenal gland.

The sudden onset of the attacks is not unlike the acute insulin insufficiency of diabetic coma, suggesting either an overwhelming wave of some toxic substance or more likely, the acute need of suprarenal substance in tissue metabolism. On this basis the sudden attacks of cyanosis suggest that the suprarenal substance may be important in the utilization of oxygen.

SUMMARY

This is a report of the clinical symptoms in a patient with bilateral thrombosis of the suprarenal veins and acute retrogressive changes of the suprarenal glands in whose body a postmortem examination did not disclose any other complicating lesion.

In addition to the usual symptoms of suprarenal insufficiency, such as asthenia, low blood pressure, gastro-intestinal disturbances and syncope, there were sudden attacks of extreme cyanosis associated with dyspnea and unconsciousness.

The suggestion is made that the cyanosis is due to suprarenal insufficiency rather than to weakness of the heart and that the suprarenal gland may play a rôle in the utilization of oxygen by the tissues.

¹³ Dietrich, A., and Siegmund, H. Die Nebenniere und das chromecaffine System, Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie, 1926, vol. 8, p. 980.

POSTINFLUENZAL BRADYCARDIA *

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Slowing of the pulse rate during the course and convalescence of certain acute infectious diseases has been a clinical observation for many years. Osler's classical description of post-typhoidal bradycardia was made in 1898, he was the first to record pulse rates as low as 30 a minute following this disease.¹ Morrison² noted the slow pulse rate in certain types of pneumonia. In 1922, Cowan and Ritchie³ were among the first to describe its development following influenzal infections.

During a recent study of postinfluenzal disturbances of the heart⁴ and postinfluenzal heart block⁵ a rather definite type of bradycardia was discovered with certain associated irregularities of rhythm, this type, though apparently common, has not been discussed in the available literature. The rather frequent occurrence of bradycardia during the recent outbreak of influenza and the apprehension aroused by its detection prompted a closer investigation of these bradycardial irregularities.

What constitutes pathologic bradycardia, so far as rate is concerned has always been a debatable question. Many healthy and active persons have a continuously slow pulse rate. An athlete under my observation has always had a pulse rate of 56. He is a long distance runner, and has completed a marathon race among the first ten. Neuhof⁶ placed the low limits of a "normal" slow pulse at 60 beats a minute, Willius⁷ considers from 50 to 60 as the lowest range in normal hearts.

In this study, when the previously known pulse rate has been higher, a rate of 60 beats a minute or lower has been used in determining cases for investigation. All together seventeen patients have been

From the Witkin Foundation for the Study and Prevention of Heart Disease, Beth David Hospital

1 Osler, William. Principles and Practice of Medicine, ed 8, New York, D Appleton & Company, 1916, p 20

2 Morrison, Alexander. Sensory and Motor Disorders of the Heart, London, 1914, p 185

3 Cowan, J, and Ritchie, W T. Diseases of the Heart, ed 2, London, 1922, p 82

4 Hyman, Albert S. Postinfluenzal Disturbances of the Heart, New York State J Med **26** 1022 (Dec 15) 1926

5 Hyman, Albert S. Postinfluenzal Heart Block. M J & Record **124** 698 (Dec 1) 1926

6 Neuhof, Selman. Clinical Cardiology, New York, The Macmillan Co, 1917, p 78

7 Willius, F A. Chronic Bradycardia, Arch Int Med **26** 630 (Nov) 1920

carefully examined and followed, but four have been selected for presentation as illustrating the various types of bradycardial irregularities which have been found in this particular group of cases

All of the patients had a rather typical attack of influenza as described by Field,⁸ with fever, malaise, generalized pains and aches, coryza and other irritations of the upper respiratory tract, headache and nausea. The relative toxemia was about the same in each case and the duration of the acute phase of the disease lasted from four to thirteen days, with a general average of about six days.

"Simple" postinfluenzal bradycardia, as indeed that which follows typhoid fever and certain types of pneumonia, is probably the result of direct poisoning of the pacemaker mechanism of the heart by bacterial toxin. A depression of the sinus node, with its specialized cells for impulse production, develops, so that there is a retardation or interference in the normal release of the stimulus necessary for exciting the cardiac contraction cycle. It is suggested that this is not purely a vagal phenomenon and the result of toxic stimulation of the autonomic system, because no other vagal effects are noted in the patient.

Many theories are current to explain the mechanism of the depression caused by the bacterial toxin. One, proposed by Wenckebach, is that the bacterial toxemia prolongs the refractory period in the sinus nodal cells in such a way that generation of the impulse is delayed. Another theory attributed to Vaquez maintains that the spread of the negative ionic wave within the nodal tissue cells is actually "neutralized" by the toxemia, and that there is thus a retardation in the summation of the negatively charged ions necessary to initiate the impulse from the node.

Clinically, this delay in the release of the impulse is noted by a slow regular pulse if the rate is from 50 to 60 beats a minute. This is demonstrated by the following case:

CASE 1—S. L., a boy, aged 11, had a usual pulse rate of from 88 to 100 with a marked sinus arrhythmia. He had an acute attack of influenza which lasted from December 2 to 7, 1926. The pulse rate on the fourth day of the disease (Dec. 5) was noted as 58 and regular. Electrocardiographic studies made on December 8 showed a normal auriculoventricular rhythm with a rate of 60 beats a minute.

On December 15, one week later, the pulse rate when the patient was at rest was 66, and after the Wolffe test with three minutes of moderate effort, the rate rose to 90. On January 6 it was 80, and on February 2, 84, with a normal electrocardiographic record.

This case illustrates a simple slowing of the pulse rate by a toxic depression of the pacemaker mechanism with a gradual recovery lasting about one month after the original attack of the influenzal infection.

8 Field, C. G. Endemic Influenza. *M. J. & Record* **123**: 125 (April 7) 1926.

Such toxic effects may be regarded as a *first degree* of nodal depression and are usually without irregularity of rhythm

Further depression of the pacemaker mechanism results in a bradycardia with a rate of from 40 to 50 beats a minute, with an irregularity which in many respects clinically may resemble a premature beat. The following case illustrates this condition

CASE 2—J. S., a man, aged 28, had a usual pulse rate of about 78. The patient had had an acute attack of influenza which lasted from Nov. 23 to 28, 1926. His pulse rate on November 28 was noted as 64, but electrocardiographic studies made on November 29 showed a rate of 46 with a slight irregularity, which on analysis was found to be due to "escaped" nodal beats. The pulse rate on December 10 was 58, on December 17, 64, on December 24, 70, and on January 10, 76.

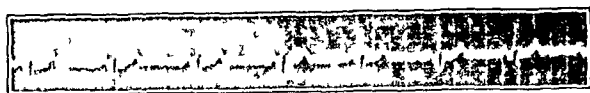


Fig. 1 (case 1)—First degree sinus depression, normal auriculoventricular rhythm with a rate of 60 beats a minute. Analysis: The P-waves are normal, the P-R interval representing conduction time from the auricles to the ventricles is constant, measuring 0.18 seconds. The Q-R-S complexes are not delayed in transmission. The T waves are upright and well formed. The T-P interval representing diastole is constant. Diagnosis: normal slow pulse.



Fig. 2 (case 2)—Second degree sinus depression (group 1), normal auriculoventricular rhythm with a "dominant" rate of 46 beats a minute, the rhythm is occasionally (from one to four times a minute) interrupted by a premature beat of sinus node origin. Analysis: The P waves are normal, the P-R interval is constant, measuring 0.16 seconds. The Q-R-S complexes are not delayed in transmission, the T waves are upright and well formed. The T-P interval while dominantly constant is interrupted by a beat which occurs too soon, that is, the distance between beats 1 and 2 and 2 and 3 is equal, but beat 4 is "premature" so far as the depressed rhythm is concerned. Actually, beat 4 is the only beat of normal rate, it has "escaped" from the depressed pacemaker mechanism. Diagnosis: Depressed nodal bradycardia with occasional escaped beats.

In this case the toxic depression of the sinus node was so great that the impulse was released at irregularly long intervals, but occasionally a stimulus escaped at what apparently was the normal rate of the pacemaker. Clinical examination of the pulse and apical beat in this condition would lead the observer to believe that the irregularity is due to a compensated, nonexhaustive extrasystole. The slow recovery to the normal pulse rate—a matter of about six weeks—indicates how long convalescence may be prolonged.

Still further depression of the nodal mechanism results in a slower pulse and a greater irregularity. Case 3 has been selected to demonstrate this finding.

CASE 3—M. L. A., a woman, aged 35, had a usual pulse rate of 84. She had an acute attack of influenza which lasted from Dec. 2 to 5, 1926. On December 5 the pulse rate was noted as 58, but on December 7 when electrocardiographic studies were made, the rate was from 40 to 46 beats a minute. Here, again, the great depression of the pacemaker mechanism resulted in a still more variable impulse release, so that a greater number of escaped beats occurred. The tracing (fig. 3) shows that nearly every other beat was so produced.

The effect on the radial pulse and the apical sounds of the heart were such that a diagnosis of frequent premature beats might easily be erroneously made. This irregularity disappeared on December 10 when the pulse rate rose to 56, on December 20 the rate was 66, and on December 28 it was 82 and regular. Of interest in this connection is the fact that while there was apparently a greater degree of depression in this case than in case 2, the period of recovery was much shorter.

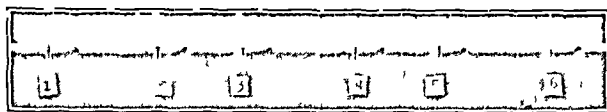


Fig. 3 (case 3)—Second degree sinus depression (group 2), normal auriculo-ventricular cycle with a "regular irregularity of rhythm." The dominant rhythm is interrupted by regular escaped beats of nodal origin so that an alternation of long and short pauses between beats is produced. Analysis: The P waves are normal, the P-R interval is constant, measuring 0.16 seconds. The Q-R-S complexes are not delayed in transmission. The T waves are upright and well formed. The T-P intervals alternate in length, that is, the diastolic period between beats 1 and 2 measures 1.34 seconds, equivalent to about 44 beats a minute. The diastolic period between beats 2 and 3 measures 1.04 seconds, equivalent to about 58 beats a minute, the diastolic period between beats 3 and 4 again measures 1.34 and that between 4 and 5 1.04 seconds and so on. After every depressed beat a normal beat tends to escape. Diagnosis: Depressed nodal bradycardia with alternation of escaped beats.

Case 4 illustrates with exceptional clearness the sequence of events which develops in any mammalian heart when the sinus node is so depressed that the impulses for auricular contraction occur at a lower rate per minute than the intrinsic impulse release from the lower or auriculoventricular node. Such idiopathic ventricular rhythms are seen in complete heart block when there has been gross destruction of the conducting system, under these conditions no impulses from the auricle reach the lower node, and as a result the lower node now initiates its own stimulus for contraction. The lower node is thus a life-saving mechanism which is called into play whenever there is a disturbance in the reception of the impulse liberated from the upper pacemaker.

9 Danielopolu D., and Proca, G. G. A-V Bradycardia. *Arch. d. mal. du coeur* 19 217, 1926.

While the normal rate of impulse release from the upper pacemaker is about 72 a minute, the lower pacemaker initiates its impulses at the much slower rate of from 28 to 40. Winterberg and Rothberger believe that the lower pacemaker of the heart is continuously forming impulses which are always discharged by the stimuli sent down by the upper pacemaker. Since the sinus node releases its impulses at a more rapid rate than the auriculoventricular node, it can be readily understood that the lower pacemaker never gets an opportunity to release its own stimuli until the upper pacemaker rate falls below its own rate or, as has been previously described in complete dissociation of the auricles and ventricles, no impulses are received from the sinus node.

When the sinus node is thus so depressed that its impulses are released at a rate of 40 a minute or less the lower pacemaker initiates its own rhythm, but it always remains subservient to those impulses from above that may chance to find the auriculoventricular node ready

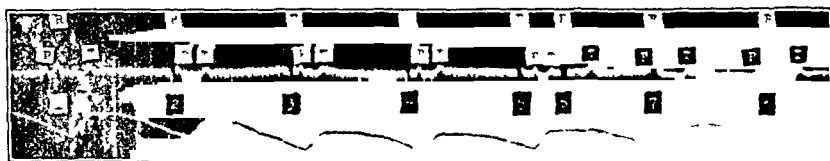


Fig 4 (case 4) —Third degree of sinus depression, depression of the pacemaker mechanism is so great that the impulse release is retarded to a rate of about 38 beats a minute. The lower auriculoventricular node with its intrinsic impulse generation of 44 beats a minute becomes the pacemaker of the heart whenever the sinus node fails to send an impulse quick enough to excite the lower node before it develops its own stimulus. The normal auriculoventricular rhythm is thus disturbed, for with the lower node assuming the role of the pacemaker, the ventricles may contract before or simultaneously with the auricles. Analysis: The P waves are well formed and upright. The P-R interval is constantly changing and is often missing as the P wave may coalesce with the Q-R-S complex as in beats 2 and 7, or it may lie between the complex and its T wave as in beats 3, 4 and 5. The Q-R-S complex is not delayed in transmission. The T wave is dominantly upright, although its first limb may become diphasic. There is no T-P interval unless the auricle happens to contract before the ventricle in its normal relationship as in beats 1 and 8. Because of the extreme depression of the sinus node, the P waves are released at a slow and somewhat variable rate (from 35 to 42 beats a minute), but the ventricular rhythm is rather constant (44 beats a minute). The radial pulse is regular with an occasional faster beat, for example, beat 6. This beat was probably developed by the P wave occurring late in the systole of the fifth beat. Diagnosis: Extreme depressed nodal bradycardia with ventricular escaped beats.

for its reception. In these cases, there is thus an interplay of the two pacemakers, a condition described by Roth as "alternation of the pacemaker mechanism." The fourth case demonstrates this interesting relation.

CASE 4—A. S., a woman aged 38, had a usual pulse rate of 74. From Dec 10 to 18, 1926, the patient had an acute attack of influenza. The pulse rate on December 14 was 58, on December 18, 52, on December 19 46 and on

December 20, 42 On December 22 the pulse became very irregular and varied in rate from 36 to 40 beats a minute. Electrocardiographic studies made on December 23 showed the interplay of the two pacemakers as described in the foregoing.

The pulse continued to be irregular until January 11, when the rate rose to 56. On January 29 the rate was 64, and on February 4 it finally returned to its previous rate of 74.

While such toxemic depressions of the pacemaker mechanism may result in these remarkable changes in pulse rate, the prognosis for complete recovery of the sinus node apparently is good in most cases although convalescence may be prolonged. In two cases not in this series which have been followed since September, 1924, no subsequent irregularity of the heart has been noted.

In contradistinction to these cases of postinfluenzal depressions of the pacemaker, the various types of heart block which may follow an acute attack of influenza must be considered.⁵ At the bedside, without the use of instrumental assistance, it may be impossible to differentiate

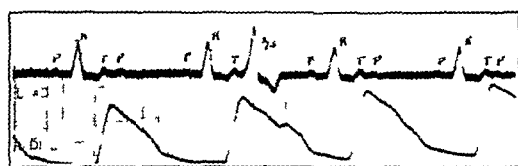


Fig. 5 (case 5)—Partial heart block with extra systoles, a 2:1 heart block with extra systoles may simulate clinically the radial pulse of a second degree of sinus depression with escaped beats. The pulse is slow (36 beats a minute) with an occasional faster (ectopic) beat. Electrocardiographic studies, however, show how dissimilar the two conditions actually are. Analysis: The P waves are upright and occur regularly at a rate of 72 a minute. Only every other P wave is followed by a Q-R-S complex. The P-R interval while slightly delayed to 0.24 seconds is constant. The Q-R-S complex is upward but delayed in transmission to 0.16 seconds, the T waves are upward. There are two P waves for each Q-R-S complex, every other auricular beat is thus blocked. An interpolated extrasystole from the right ventricle occurs after the second beat, it is effective in opening the aortic valves. Hence, it is felt in the radial pulse as an "extra" beat. Diagnosis: 2:1 partial heart block with right ventricular extrasystoles.

the bradycardial irregularities due to toxemic depression of the pacemaker and those due to partial or complete heart block with extrasystoles. Such cases are presented for comparison.

CASE 5—J. S., a man, aged 51, had a history of heart disease. After a rather severe attack of influenza in which he was markedly prostrated, his pulse rate fell to about 32 beats a minute, with a distinct irregularity. Physical examination of the radial pulse and auscultation of the heart gave observations similar in many respects to those noted in the cases of second and third degree of sinus depression described in the foregoing. Graphic records readily demonstrated, however, that the condition was actually one of 2:1 heart block with extrasystoles arising from the right ventricle.

The need for accurate diagnosis is rather important, for while sinus nodal depression is relatively innocuous postinfluenzal heart block of

this type with extrasystoles has an ominous prognosis. Electrocardiographic and polygraphic studies in such conditions are of the utmost importance.

While a slow, regular radial pulse may often accompany complete heart block with dissociation of auricular and ventricular rhythms, a bradycardial irregularity may occur similar clinically to that due to both sinus nodal depression and partial heart block. Here again extreme refinement in diagnosis may be and often is necessary, careful instrumental methods may be essential for the complete understanding of the process. Such a case is demonstrated by the following case.

CASE 6—In a woman, aged 61, an attack of influenza had caused more decompensation of an already damaged myocardium. The pulse rate which before the attack had been from 90 to 104 now fell to 28 with frequent irregularity.

A diagnosis of complete heart block was made from the graphic records, and the prognosis based on the information received from the tracings was extremely bad, in fact, the patient died about two weeks after the aforementioned record was taken.



Fig 6 (case 6)—Complete heart block, dissociation of auricular and ventricular rhythms simulating a third degree of sinus node depression with ventricular escaped beats. In this case the auricles and ventricles have assumed independent rates without relation to each other. The radial pulse is slow (42 beats a minute) and regular occasionally interrupted by a faster beat. Clinically, the pulse suggests that of both second and third degrees of sinus node depression. Analysis: The P waves are upright and occur regularly at a rate of 82 a minute. There is no relation between the P waves and the Q-R-S complexes, no auricular impulses ever reach the auriculoventricular node. The Q-R-S complexes are downward and of different heights, due apparently to a respiratory rotation of the electric axis of the heart. The complex is delayed in transmission to about 0.16 seconds. The P wave is upright. The ventricular complexes occur almost regularly at a rate of 42 beats a minute interrupted by an occasional faster beat. Diagnosis: Complete heart block.

COMMENT

Certain infectious diseases, of which influenza must be considered the most common, apparently produce toxic substances that specifically poison the pacemaker mechanism of the heart. These toxic substances, instead of accelerating the pulse rate, as is usually the case in infectious conditions with pyrexia, seem to depress the production of the stimulus in the sinus nodal cells so that a slowing of the pulse rate results. There is no evidence that the slowing is the result of vagal stimulation.

Three degrees of depression of the sinus node seem to occur. The first consists of a simple slowing of the pulse rate to about 60 beats a minute when the previously normal rate has been from 74 to 88. The

second degree of depression of the pacemaker mechanism produces a bradycardia of from 40 to 50 beats a minute with an irregularity which in many respects clinically suggests an extrasystole, but which on instrumental investigation is discovered to be escaped nodal beats. Further depression apparently results in the escape of more such beats to the extent that every other impulse may be so produced. The third degree of nodal depression is so extreme that the Gallavardin phenomenon of independent ventricular rhythm occurs¹⁰ with an irregularly slow pulse of from 28 to 38 beats a minute.

The clinical importance of detecting this condition cannot be over-emphasized, for it may be readily confused at the bedside with partial and complete heart block associated with extrasystoles. While toxic depression of the pacemaker mechanism is relatively innocuous and apparently leaves the heart undamaged, heart block of the second and third degrees following an acute infectious disease usually suggests extensive mischief suffered by the conducting system and perhaps irreparable myocardial injury.

Prognosis in the latter condition must necessarily be rather guarded, and the patient's activities closely supervised, while the outlook in toxic nodal depression is apparently good with complete recovery of the cardiac condition expected.

The differential diagnosis of such clinically similar cardiopathies may be extremely difficult and at times impossible. For this reason it may be suggested that all bradycardial irregularities, more especially those following acute infectious diseases like influenza, should be investigated by electrocardiographic and polygraphic studies to determine the true condition of the cardiac mechanism. In this way, the number of sudden deaths and other cardiovascular accidents which seem to be increasing daily may, perhaps, be avoided.

10 Gallavardin, L., and Gravier, L. Bradycardie Nodale Permanente, Etude du Rhythm Atrio-ventriculaire, Arch d mal du coeur **14** 71, 1921.

Book Reviews

THE FIFTH AVENUE HOSPITAL CLINICS Price \$5 New York Paul B Hoeber, 1927

This book includes twenty-six articles by the attending staff of the Fifth Avenue Hospital, New York City. Many of the papers were given at the semi-monthly staff meetings, the remaining articles are reprints published in connection with cases in the hospital. The papers cover many fields of medicine and surgery and are arranged chronologically in the order in which they were presented at the various staff meetings.

This book represents a splendid effort on the part of the attending staff to encourage more careful study of the clinical material in the hospital and to increase the value of the staff meetings.

X-RAY DIAGNOSIS By J MAGNUS RÖDING Price \$7 New York William Wood & Company, 1927

The author addresses two hundred and twenty-eight pages on general roentgen-ray diagnosis to the surgeon, practitioner and student. The subject matter is systematic, up to date, and covers a wide scope. The intention is to give short discussions on the many phases of roentgen-ray diagnosis, rather than an exhaustive review of any one. From this point of view the book shows admirable balance and a wealth of experience on the part of the author.

The book is profusely illustrated with well selected roentgenograms. An attempt has been made to illustrate the important and typical lesions as far as possible and to omit the rare and bizarre. This makes it especially valuable for the student and general practitioner.

HAMATOLOGISCHES PRAKTIKUM By HANS ZIFMANN Pp 166, with 34 illustrations and 3 colored charts Price, 7.20 marks Berlin S Karger, 1927

This booklet, in German, is intended for students and practicing physicians as a guide in the clinical examinations of the blood. It contains directions for making the usual cell counts and the stained preparations of the blood. It gives the normal conditions and describes the abnormal. Anemia and Leukemia are described, and with the latter are considered a variety of diseases in which there is an enlargement of the lymph nodes. Various parasitic diseases of the blood, certain pathologic conditions of the spleen, differential diagnosis, and therapeutic measures in some of the diseases are discussed. A summary concludes the volume.

The information obtained will scarcely compensate those who have little knowledge of German for their difficulty in reading the book, certain American laboratory texts contain in a more accessible form all of the material presented in this work.

CALCIUM STUDIES IN JAUNDICE

WITH SPECIAL REFERENCE TO THE EFFECT OF PARATHYROID
EXTRACT ON THE DISTRIBUTION OF CALCIUM*

A CANTAROW, M D

S M DODEK, M D

AND

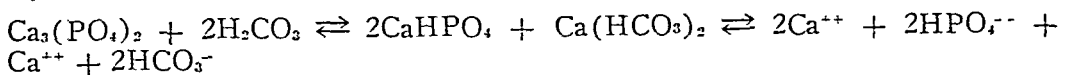
BURGESS GORDON, M D

PHILADELPHIA

In recent years considerable progress has been made in the study of jaundice, but comparatively little is known about the details of the chemical processes involved. The tendency to prolonged bleeding in jaundiced patients has long been known. Obviously this fact is of practical importance, since it adds greatly to the operative risk in a condition that often requires surgical treatment. It is generally believed that the hemorrhagic tendency is intimately related to some fault in the availability and utilization of calcium, although the exact mechanism is far from being well understood.

REVIEW OF PREVIOUS OBSERVATIONS

Calcium exists in the blood stream in several forms—ionized and unionized, diffusible and nondiffusible, free and combined. According to Howland,¹ calcium phosphoric acid and carbon dioxide are present in the blood in a finely balanced equilibrium, illustrated by the following equation:



Wells² states that the calcium salts are held partly in solution, partly in suspension and partly in the form of calcium ion protein compounds. This condition is extremely unstable, it is subject to alteration by slight changes in any of the several controlling factors. In addition, it is now recognized that the parathyroid hormone plays an important part in the maintenance of the normal calcium level and distribution.

* From the Medical Service of Dr. Thomas McCrae and the Department for Diseases of the Chest, Jefferson Hospital.

* A part of the expense for this investigation was defrayed by a grant from Mr. L. A. Swayze, of Canton, Pa.

* Read before the College of Physicians of Philadelphia, June 1, 1927.

1 Howland, J. Etiology and Pathogenesis of Rickets, Harvey Lectures 18, 189, 1922-1923.

2 Wells, H. G. Chemical Pathology, Philadelphia, W. B. Saunders Company, 1925, p. 492.

Kirk and King³ have shown that normally all the common inorganic constituents of serum are diffusible except calcium, of which only from 70 to 75 per cent is diffusible. Grove and Vines⁴ state that calcium is present in ionized and combined forms, but that under normal conditions only the ionized form is found in the serum after coagulation, which suggests the importance of combined calcium in the mechanism of coagulation. With such a variety of factors operating to maintain the normal relations of calcium in the blood stream, it is evident that a disturbing element may exercise its effect in several ways. Anything that will alter the calcium level, the hydrogen ion concentration, the phosphate and the carbon dioxide content, the amount and nature of the proteins, the ratio of diffusible to nondiffusible calcium and of the ionized to the combined forms will cause some disturbance in the functional availability and utilization of calcium. This, however, is not necessarily manifested by any change in the phenomenon of coagulation.

The characteristic feature of jaundice is the presence of an excess of bile pigments and bile salts in the blood. Interference with the normal mechanism of coagulation is perhaps due to the action of these substances, although in advanced cases, hepatic malfunction may play a part through the associated diminution in the formation of fibrinogen. Prolongation of the coagulation time does not occur in all patients with jaundice. Lee and Vincent⁵ state that it is met with only to a slight extent in catarrhal jaundice. These authors have observed no change in coagulation time until the jaundice was of five weeks' duration, and they conclude that such change depends on the intensity of the condition and the amount of available tissue calcium. However, as is well known, the hemorrhagic tendency in jaundice is not incompatible with a normal clotting and bleeding time.

Haessler and Stebbins⁶ believe that in some way the bile salts retard the conversion of fibrinogen to fibrin. This factor possibly plays a minor part, however, and for our purposes may be disregarded. Interest is particularly focused on the alteration in the distribution and functional availability of calcium caused by the presence of abnormal amounts of bile pigments in the blood and tissues.

The exact manner in which the pigments operate to diminish the available circulating calcium is unsettled. King and Stewart⁷ report

3 Kirk, P. L., and King, C. G. Calcium Distribution in the Blood, *J. Lab. & Clin. Med.* **11** 928 (July) 1926.

4 Grove, W. R., and Vines, H. W. C. Calcium Deficiency and Treatment by Parathyroid Extract, *Brit. M. J.* **1** 791 (May 20) 1922.

5 Lee, R. I., and Vincent, B. The Relation of Calcium to the Delayed Coagulation of Blood in Jaundice, *Arch. Int. Med.* **16** 59 (July) 1915.

6 Haessler, H., and Stebbins, M. G. Effect of Bile on Clotting Time of Blood, *J. Exper. Med.* **29** 445, 1919.

7 King, J. H., and Stewart, H. A. Effect of the Injection of Bile on the Circulation, *J. Exper. Med.* **11** 673, 1909.

that the blood calcium is increased in jaundice owing to obstruction. This observation was confirmed by King, Bigelow and Pearce⁸. They believe that calcium combines with the pigments as a protective measure in an attempt to counteract their toxicity. This combination appears to fix the calcium in some way and to render it functionally unavailable, probably by lessening the degree of diffusibility and ionization. Kirk and King³ have found that whereas normally 72.3 per cent of the blood calcium is diffusible, in jaundice this fraction is reduced to 55.2 per cent. They state that the percentage of diffusible calcium in jaundice is subnormal, roughly, in proportion to the degree of jaundice. They add that this is not the only factor that increases the coagulation time, as similar changes in diffusibility occur in other conditions without affecting coagulation.

It is not unlikely that the nature and amount of blood proteins are of importance in this connection. In certain forms of hemolytic jaundice and in some cases of pernicious anemia the bilirubin content of the blood may be far above the normal renal threshold concentration without appearing in the urine. Bowler and Walters⁹ believe that the pigment in such cases is fixed to the plasma proteins to some extent, lessening the diffusibility of the pigment molecule and preventing its excretion. The protein-pigment combination, uniting with calcium, increases the ratio of protein bound to free calcium, altering the normal diffusibility and ionic relations.

When pigment deposition occurs, a considerable amount of calcium which is normally circulating and utilized is fixed in the tissues. Early in the condition this fixation is counterbalanced by the normal calcium reserves, but as the intensity progresses and the degree of fixation increases, these reserves become relatively depleted, and in a functional sense, an actual calcium deficiency occurs. This accounts for the fact, observed by Lee and Vincent,⁵ that early in jaundice there is no change in coagulation time. As they state, such alteration is largely dependent on the amount of calcium in the tissues that can be taken into the blood.

In an attempt to supply this deficiency in jaundice, calcium therapy has been employed with variable results. The success of oral administration is dependent on so many factors that uniformly good results cannot be expected. Lee and Vincent⁵ report that large doses of calcium lactate must be given over a period of several days before any alteration in clotting time occurs. Bowler and Walters¹⁰ use small amounts of calcium chloride intravenously for a short period before

8 King, J. H., Bigelow, J. E., and Pearce, L. Experimental Obstructive Jaundice, *J. Exper. Med.* **14** 159, 1911.

9 Bowler, J. P., and Walters, W. Toxicity and Rate of Excretion of Calcium Chloride from the Blood Stream, *Ann. Surg.* **80** 545, 1924.

10 Walters, W., and Bowler, J. P. Preoperative Preparation of Patients with Obstructive Jaundice, *Surg. Gynec. Obst.* **39** 201, 1924.

operation, with apparent success. They report the interesting observation that twice the amount of calcium chloride injected intravenously is required to raise the blood serum calcium in jaundice to the same level as in normal persons. This, as they say, suggests a calcium deficiency that is not otherwise apparent.

Parathyroid extracts have been proved to exert a profound influence on calcium metabolism. Their administration results in an increase in the amount of available circulating calcium and also perhaps aids in its utilization. In a previous study¹¹ we observed the changes in the calcium content of the whole blood and of serum at three hour intervals following the injection of parathyroid extract. The results in six normal cases are shown in table 1. It was noted that the rise in serum calcium generally preceded that in whole blood. Furthermore, it was observed that the curve of whole blood calcium differs materially from that of serum, but corresponds more exactly than the latter to the curve

TABLE 1—*Coincident Determinations of the Whole Blood and Serum Calcium in Nonjaundiced Patients at Three Hour Intervals Following the Administration of Parathyroid Extract*

Case	Control		3 Hours		6 Hours		9 Hours		12 Hours	
	Blood*	Serum*	Blood	Serum	Blood	Serum	Blood	Serum	Blood	Serum
1	7.64	10.1	7.7	15.7	9.8	11.4	10.05	11.4	12.24	10.9
2	6.43	10.45	11.36	10.22	10	9.04	10.23	10.4	8.62	10.24
3	6.6	10.2	6.2	11.3	8.1	11.3	8.1	10.8	11.1	9.6
4	6.52	10.43	5.7	14.54	9.52	11.4	11.2	11.04	10.34	10.76
5	9.54	10.45	11.99	10	12.2	9.5	9.8	10.78	8.07	9.13
6	9.61	10.09	10.09	10.09	10.52	8.8	11.17	9.52	8.18	9.04

* Calcium values are expressed in milligrams per hundred cubic centimeters

of changes in the coagulation time. From this we concluded that the whole blood or plasma calcium content was a more accurate index of changes in the blood following the administration of parathyroid hormone than the serum calcium.

METHODS

The method used for the determination of whole blood calcium¹² was based on the Clark-Collip modification of the Kramer-Tisdall method for determining serum calcium¹³. The figures are undoubtedly higher than the actual calcium content, owing to the reaction of certain constituents of the stroma of the corpuscles. However, the method was

11 Cantarow, A., Caven, W. R., and Gordon, B. Changes in the Chemical and Physical Characteristics of the Blood Following the Administration of Parathyroid Hormone, *Arch. Int. Med.* **38**: 502 (Oct.) 1926.

12 Caven, W. R., and Cantarow, A. A Method for the Determination of Calcium in Whole Blood, *J. Lab. & Clin. Med.* **12**: 76 (Oct.) 1926.

13 Clark, E. P., and Collip, J. B. A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, *J. Biol. Chem.* **63**: 461 (March) 1925.

used to obtain a curve showing the changes in blood calcium after the injection of parathyroid extract rather than to determine the absolute calcium values. It was found satisfactory for this purpose, since the error was a constant one. This was proved subsequently by simultaneous determinations of plasma calcium, coagulation being retarded by the use of heparin¹⁴. The curve showing the changes in the plasma calcium was found almost to parallel that of the whole blood.

The present investigation was undertaken to compare the response to parathyroid extract¹⁵ in jaundiced and in normal persons. The series consists of fourteen cases of jaundice, one was hemolytic in type, three were cases of hepatitis due to arsphenamine and ten were of an obstructive nature, resulting from either gallstones or carcinoma of the head of the pancreas. The intensity of the jaundice varied from 2 to 20 units.

TABLE 2—*Coincident Determinations of the Whole Blood and Serum Calcium in Jaundice at Three Hour Intervals Following the Administration of Parathyroid Extract*

Case	Type	Units	Control		3 Hours		6 Hours		9 Hours		12 Hours	
			Blood*	Serum*	Blood	Serum	Blood	Serum	Blood	Serum	Blood	Serum
1	Hemolytic†	2	10.45	10.45	12.72	11.86	11.17	9.6	9.16	9.31	10.26	8.7
2	Obstructive	16	10.59	10	9.54	9.54	10.18	9.8	10.53	8.43	12.5	9.13
3	Obstructive	10	12	10.02	11.8	10.8	11.2	14.1	11.6	12		
4	Obstructive	3	11	9.52	10.5	7.6	13	10	12	10		
5	Obstructive	15	4.8	10	7.9	10	10.9	10.9	11.6	10.9		
6	Obstructive	20	7.5	9.3	8.5	9.7	8.8	9.7	9.7	9.7	8.5	9.7
7	Obstructive	8	8.1	9.55	11.86	9.62	11.47	11	14.75	10.4		
8	Obstructive	7	8.2	11.3	10.2	12.1	11.5	12.4	10	11.6		
9	Obstructive	10	4.9	10.8	9.1	13.1	11.3	12.2	8.4	10		
10	Obstructive	15	8.2	9.3		10		10		9.7		
11	Obstructive	10	10.96	10.32								
12	Toxic hepatitis‡	8	4.9	10.5	12	11	12.4	11	11.7	9		
13	Toxic hepatitis	14	7.6	12	8.3	13	8.3	13.5	10	13.5	10.5	14.1
14	Toxic hepatitis	4	8.2	9.5		9.5		10.5		10.4		

* Calcium values are expressed in milligrams per hundred cubic centimeters.

† Amount of bilirubin expressed in units by the van den Bergh method.

‡ Caused by arsphenamine.

of bilirubin as determined by the van den Bergh test. The following determinations were made: clotting time by the Boggs method, and the calcium content of whole blood,¹² serum¹³ and, in some instances, plasma. After one control observation the determinations were repeated at three hour intervals following the intramuscular injection of parathyroid extract. The figures for calcium are presented in tables 2 and 3.

RESULTS OF AUTHORS' INVESTIGATIONS

Coagulation Time—The clotting time in all cases before administration of parathyroid hormone was well within normal limits. It ranged between three and five minutes, with apparently no relation to the depth.

14 Plasma determinations were made by the Clark-Collip method, powdered heparin being used to prevent coagulation in the specimen of blood.

15 The preparation used was para-thor-mone, supplied by Eli Lilly and Company through the kindness of Dr. G. H. A. Clowes and Dr. J. H. Warvel.

duration or type of jaundice. The response to the administration of the hormone was similar to that previously observed in persons who were not jaundiced¹¹. The clotting time was reduced in all instances, the degree of reduction varying between 5 and 65 per cent. The maximum effect occurred from six to twelve hours after the injection. The rapidity of coagulation did not bear as close a relationship to the whole blood calcium as it did in the normal cases, but it still appeared to be much more dependent on this factor than on the serum calcium level.

Serum Calcium—The normal range of serum calcium is from 9 to 11 mg per hundred cubic centimeters. The control values in the normal cases were from 10.09 to 10.45 mg. After the administration of parathyroid extract, there was a tendency toward a rise in serum calcium within the first three hours, followed by a gradual return to normal (table 1). The maximum variation occurred three hours after the injection.

TABLE 3—*Coincident Determinations of the Whole Blood, Plasma and Serum Calcium in Jaundice at Three Hour Intervals Following the Administration of Parathyroid Extract*

Case	Control			3 Hours			6 Hours			9 Hours			12 Hours		
	Blood*	Plasma*	Serum*	Blood	Plasma	Serum	Blood	Plasma	Serum	Blood	Plasma	Serum	Blood	Plasma	Serum
8	8.2	14.1	11.2	10.2	17.6	12.1	11.5	18.7	12.4	10	17.1	11.6			
9	4.9	8.8	10.8	9.1	17.6	13.1	11.3	20.1	12.2	8.4	16.1	10			
10	8.2	9.6	9.3		12	10		12	10		11.9	9.7			
11	10.96	18.01	10.32												
13	7.6	17.8	12	8.3	18.2	13	8.3	19	13.5	10	19.5	13.5	10.5	20.3	14.1
14	8.2	12.5	9.5		15	9.5					15.2	10.4			

* Calcium values are expressed in milligrams per hundred cubic centimeters

In the series of patients with jaundice the control values varied slightly beyond normal limits, from 9.3 to 12 mg per hundred cubic centimeters. The response to parathyroid hormone was inconstant, in some instances no rise occurred, in others there were slight rises at varying intervals. We do not attach significance to the absence of an increase in calcium in several cases, since the rise may have occurred in an interval between our determinations. However, the results are interesting when compared with those of normal persons as illustrated in chart 1. It is seen that the limits of variation in serum calcium are slightly affected by parathyroid extract in jaundiced persons as compared with normal persons.

Whole Blood—The whole blood calcium in the normal group varied between 6.43 and 9.61 mg per hundred cubic centimeters¹². After the administration of parathyroid extract, there was a gradual tendency toward an increase in the blood calcium level, the degree of variation

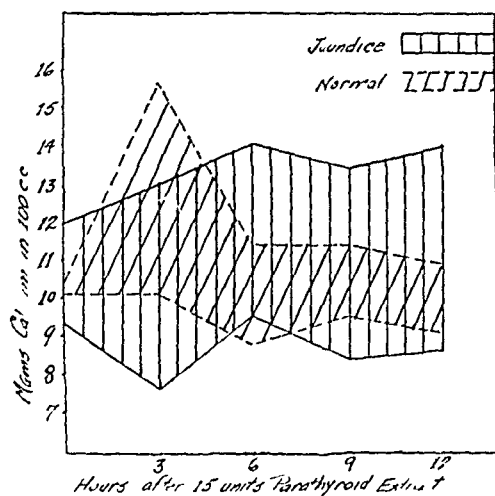


Chart 1—Comparison between the variation in serum calcium in jaundiced and in normal persons before and at three hour intervals following the administration of parathyroid extract. The area occupied by diagonal lines represents variation between minimum and maximum serum calcium values in normal persons, the area occupied by perpendicular lines represents variation between minimum and maximum serum calcium values in jaundice.

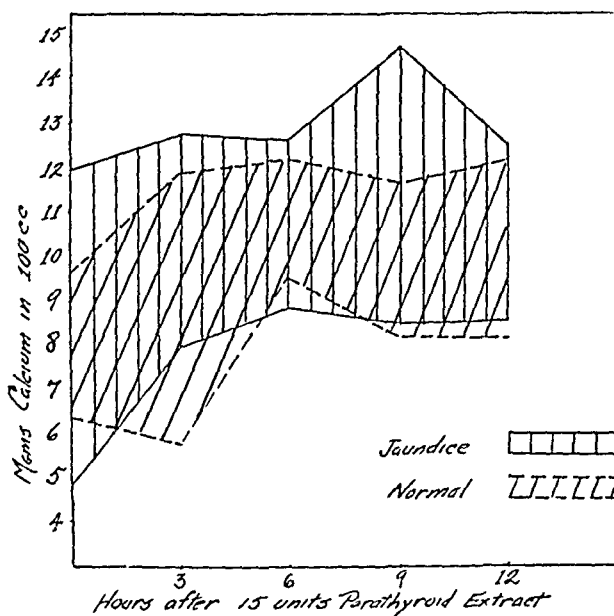


Chart 2—Comparison between the variation in whole blood calcium in jaundiced and in normal persons before and at three hour intervals following the administration of parathyroid extract. The area occupied by diagonal lines represents variation between minimum and maximum whole blood calcium values in normal persons, the area occupied by perpendicular lines represents variation between minimum and maximum whole blood calcium values in jaundice.

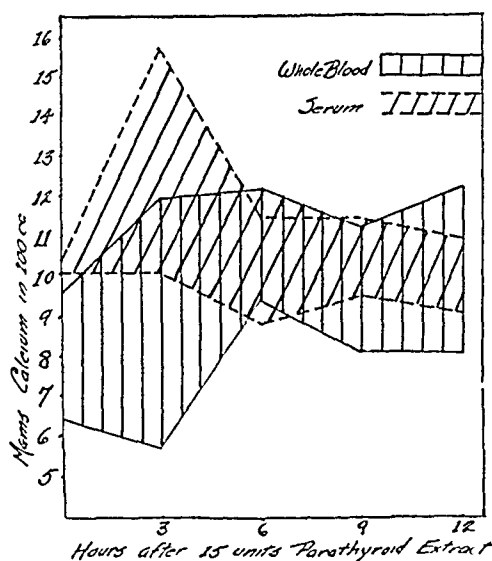


Chart 3—Comparison between the variation in serum and whole blood calcium in normal persons before and at three hour intervals following the administration of parathyroid extract. The area occupied by diagonal lines represents variation between minimum and maximum normal serum calcium values, the area occupied by perpendicular lines represents variation between minimum and maximum normal whole blood calcium values.

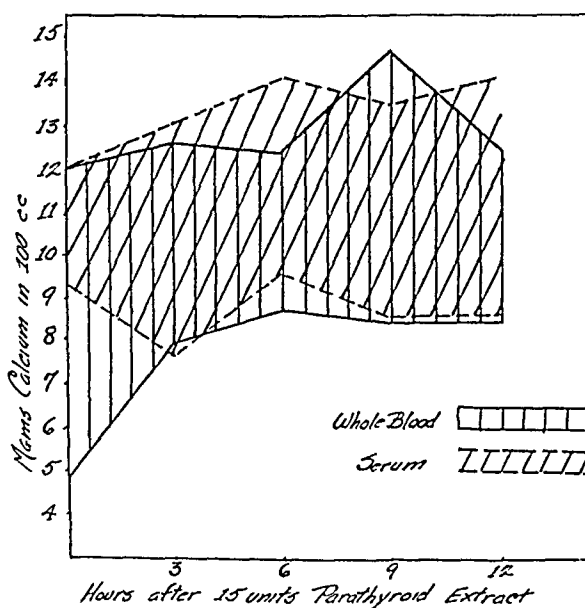


Chart 4—Comparison between the variation in serum and whole blood calcium in jaundice before and at three hour intervals following the administration of parathyroid extract. The area occupied by diagonal lines represents variation between minimum and maximum serum calcium values in jaundice, the area occupied by perpendicular lines represents variation between minimum and maximum whole blood calcium values in jaundice.

remaining approximately the same as before. In the jaundiced patients the control values for blood calcium ranged between 4.8 and 12 mg per hundred cubic centimeters. This wide variation was the first striking difference observed between jaundiced and normal blood. The calcium level bore no relation to the coagulation time, degree, type or duration of the jaundice. The injection of parathyroid extract was followed by a marked decrease in the degree of variation, at the end of six hours, and particularly after twelve hours, the range in jaundiced persons was practically identical with that in normal persons (chart 2). The relationship between whole blood and serum variations in normal and in jaundiced persons is illustrated in charts 3 and 4.

Plasma Calcium—In some cases the calcium content of the plasma was determined. It varied between 8.8 and 18.01 mg per hundred cubic centimeters in the group of patients who had jaundice. The determinations after parathyroid administration were almost exactly parallel to those of whole blood.

COMMENT

In reviewing these data several interesting facts might be noted. However, there are two points which to us seem of particular significance: first, the wide variation in the calcium content of whole blood in jaundice as compared with that of normal blood; second, the fact that after the administration of parathyroid extract this variation is altered, so that at the end of twelve hours the calcium content of the blood corresponds almost exactly to that in normal persons treated in the same manner (chart 2).

The variation in the calcium content of whole blood is undoubtedly of considerable significance. We have stated that the amount seems to be independent of the type, intensity and duration of the jaundice, and that it bears no relation to the coagulation time. Of still greater interest is the fact that it is equally independent of the serum calcium content (table 2). For example in case 2 the patient had a whole blood calcium of 10.59 mg and in case 5, 4.80 mg. The serum calcium content in both cases was 10 mg per hundred cubic centimeters. It seems obvious that the amount of calcium which participated actively in the process of coagulation, and which perhaps was incorporated in the clot in protein or lipodol combination, differed greatly in the two instances, being comparatively large in case 2 and slight in case 5. This relative fixation of serum calcium irrespective of the blood calcium level is in all likelihood due to the presence of the bile pigments, which bind the calcium, rendering it functionally unavailable. Since most of the pigment remains in the serum after coagulation, the bound calcium likewise remains. This tends to maintain the relative constancy of the serum calcium values as compared with those of whole blood in jaundice. The wide

variation in the blood calcium must be dependent largely on corresponding variations in the general calcium metabolism of the tissues, in the functionally available and diffusible fractions and in the amount fixed in the tissues by the pigments and excreted with them in the urine. The supposition of functional deficiency is supported by the work of Bowler and Walters¹⁰ referred to previously, in which they observed that much more calcium chloride, given intravenously, is necessary to raise the serum calcium in jaundice to the same level as in normal persons.

The effect of parathyroid extract on the distribution of blood calcium in jaundice is striking. Collip states¹⁶ that in the normal animal the function of the parathyroid hormone "appears to be that of a regulator of calcium metabolism, and its action is primarily as a calcium mobilizer." We have shown that in jaundice there is a disturbance of calcium metabolism of varying degree, evidenced by the abnormal distribution of calcium in the blood stream. In twelve hours after the administration of parathyroid extract the distribution of calcium is temporarily practically identical in jaundiced and in normal persons. Evidently the hormone tends to restore the normal balance between blood and tissues in an attempt to remedy the existing functional deficiency. One evidence of the success of this attempt is the reduction of the coagulation time, suggesting an increase in the availability and utilization of the calcium of the blood. Though increasing the functionally available calcium the tendency to slow, protracted hemorrhage of a diffuse nature may be lessened, as noted in incised tissues in jaundice often associated with a normal coagulation and bleeding time. As previously suggested, this favorable effect is perhaps due¹⁷ to a decrease in the permeability of the capillary walls, aided, undoubtedly, by the increased coagulability of the blood following administration of parathyroid extract.

CONCLUSIONS

1 In jaundice it is evident that a functional deficiency in calcium exists probably due to the increased amount of bile pigments in the blood and tissues.

2 The calcium content of whole blood, plasma and serum and the coagulation time have been determined at three hour intervals after the injection of parathyroid extract. The observations in jaundice are compared with those in nonjaundiced persons.

3 The serum calcium values varied slightly, ranging from 9.3 to 12 mg per hundred cubic centimeters in jaundice. There was an

16 Collip, J. B. The Calcium Mobilizing Hormone of the Parathyroid Glands, *J. A. M. A.* **88** 566 (Feb. 19) 1927.

17 Gordon, B., and Cantarow, A. The Use of Parathyroid Extract in Hemorrhage, *J. A. M. A.* **88** 1301 (April 23) 1927.

extremely wide variation, however, in the calcium content of whole blood, the figures ranging between 4.8 and 12 mg per hundred cubic centimeters

4 Twelve hours after the administration of the parathyroid hormone the variation in the whole blood calcium of jaundiced and nonjaundiced patients was practically identical

5 Parathyroid extract acts as a mobilizer of calcium, in jaundice it tends to restore the normal distribution and functional availability of this element

6 The favorable effect of the hormone on the tendency of jaundiced tissue to bleed is due largely to the increased coagulability of the blood and probably to the diminished permeability of the capillary walls, the result of an increase in functioning calcium

THE STORAGE OF WATER BY VARIOUS TISSUES OF THE BODY^{*}

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While it is well known that water plays an extremely important rôle in the economy of the body, and that it is the most abundant constituent, making up 90 pounds (40.8 Kg) of a man weighing 143 pounds (64.9 Kg), there have been few investigations concerning the exact distribution of this water in the animal as a whole, although the water content of many individual organs has been determined.

The purpose of my work is to show the distribution of the water in mammals and to determine whether there are water depots in the body similar to the glycogen and fat depots, and, if such exist, to study a few of the factors influencing the storage or discharge of fluids from them. My purpose is also to determine the relative importance of the different tissues of the body as water depots.

DISTRIBUTION OF WATER IN MAMMALS

All tissues contain water, even the enamel of teeth. Blood, lymph, digestive juices, urine, sweat, feces and expired air are from 80 to 90 per cent water, the organs and softer tissues, about 75 per cent.

Table 1 shows the percentage of water in the body and in the different organs in relation to their weight, for man, rat, dog, cat and rabbit. This table reveals that the water content of the corresponding organs in the different animals is approximately the same. If one should examine the literature cited, one would find that the differences in the water content of the corresponding organs between man and these animals (excepting only a few instances) do not vary more than the figures given by the different authors for the organs of man. Particular attention is called to the small differences between the figures for man, for the cat and for the rabbit. It is also shown that the tissues containing the highest percentage of water are those which are concerned with the transportation of water, and which are under continuous activity, that is, the blood and the heart, also those concerned in the excretory process, namely, the lungs and the kidneys.

The tissues having the lowest percentage composition of water, such as the skeleton and the skin, form the framework and protective covering of the body. The liver also ranks among those being low in water content.

The intestine and skeletal muscle rank intermediate to the other tissues and organs.

^{*} From the Department of Physiology, University of Minnesota.

TABLE 1—Percentage of Water in Organs in Relation to Their Weight

Organs	Man*	Rat†	Dog‡	Cat§	Rabbit¶
Skin	72.03	77.1	58.9	68.3	71.4
Muscles	75.67	76.2	73.5	74.5	75.08
Skeleton	22.04	47.4	31.66	32.8	20.54
Brain	74.84	77.5	75.03	78	77.93
Spinal cord		69.13	69.53		69.42
Liver	68.25	74	73.7	67.9	75.8
Heart	79.21	77.6	78.39	78.46	78.58
Lungs	78.96	81.6	78.7	76.3	77.65
Kidney	82.68	77.1	76.72	75.3	78.86
Spleen	75.77	77.4	78.6	78.2	80
Blood	83	80.82	82.8	86.7	82.8
Intestine	74.54	76.36	75.4	78.3	78.4
Entire body	63	65.3	65.7	64.2	68.8

* Bischoff, E. Ztschr. f. rat. Med. **20** 75, 1863. Engles, W. Arch. f. exper. Path. u. Pharmacol. **51**, 346, 1904. Herman, L. Handbuch der Physiologie **6** 345, 1891.
† Donaldson, H. H. Memoirs of the Wistar Institute, Philadelphia, 1915.
‡ Engles, W. Arch. f. exper. Path. u. Pharmacol. **51** 346, 1904. Stewart, G. N. Am. J. Physiol. **58** 45, 1921.
§ Voit, von Carl. Ztschr. f. Biol. **2** 353, 1866.
¶ Krause, W. Zweite Auflage, Leipzig, 1884.

TABLE 2—Percentage Weight of Organs in Relation to Body Weight*

Organs	Man	Rat	Dog	Cat	Rabbit
Skin	18	18.01	16.11	13.94	13.2
Muscle	41.7	45.4	42.84	45.36	52.2
Skeleton	15.9	10.9	17.39	12.67	12.4
Brain	2.01	0.46	1.37	1.04	0.58
Spinal cord		0.16		0.07	0.18
Liver	2.26	4.17	3.6	2.96	5.2
Heart	0.47	0.34	0.81	0.37	0.88
Lungs	0.69	0.53	0.88	0.51	1.24
Kidneys	0.37	0.78	0.65	0.81	0.71
Spleen	0.18	0.25	0.22	0.28	0.1
Blood	4.9	5.5	7	4.46	6.75
Intestine	1.81	3.96	6.5	3.8	4
Rest of body	4.63	2.89	2.63	4.1	1.88

* The footnotes for this table are the same as those for table 1, with the exception of those referring to the column on "Man," which are as follows: Bischoff, E. Ztschr. f. rat. Med. **20** 75, 1863. Engles, W. Arch. f. exper. Path. u. Pharmacol. **51** 346, 1904.

TABLE 3—Distribution of Water to Various Organs as Computed from Values Set Forth in Tables 1 and 2 When Body Weights Are Man, 65 Kg, Rat, 450 Gm, Dog, 4 Kg, Cat, 2 Kg, Rabbit, 2.5 Kg

Organs	Man		Rat		Dog		Cat		Rabbit	
	O W	G W	O W	G W	O W	G W	O W	G W	O W	G W
Skin	11,700	8,437.5	81	62.45	644.4	379.5	278.8	190.4	330	235.6
Muscle	27,105	20,510	204	155.6	1,713.6	1,259	907.2	675.8	1,305	979.7
Skeleton	10,335	2,277	49	23.2	695.6	220.2	253.4	83.1	310	63.6
Brain	1,306	977.7	2	1.6	54.8	41.1	20.8	20.5	14.6	11.3
Spinal cord			0.7	0.5			5.4		4.7	3.2
Liver	1,469	1,002.5	18.7	13.8	144	106.1	59.2	40.1	130	98.5
Heart	305.5	241.9	1.5	1.1	32.4	25.3	7.4	5.8	22	17.2
Lungs	448.5	334.1	2.3	1.9	35.2	27.7	13.8	10.5	31	24
Kidneys	240.5	198.8	3.5	2.7	26	19.9	7.4	5.5	17.7	13.9
Spleen	117	88.6	1.1	0.9	8.8	6.9	3.6	4.3	2.5	2
Blood	3,195	2,651	24.7	20	280	231.8	89.2	77.3	168.7	139
Intestine	1,176.5	876.9	17.8	13.6	260	196	78	59.5	100	78
Rest of body		6,046		6.1		114		11.4		51.3
Total		40,950		293.8		2,628		1,284		1,171

O W indicates weight of organ in grams, G W, grams of water in the organ

Table 2 is a tabulation of the percentage weights of various organs of man, rat, dog, cat and rabbit in relation to body weight. Attention is again directed to the fact that this weight in the different animals does not vary any more than the figures for any one organ within the same species.

The weights of the different organs and the grams of water each contains in the individual animals of a given weight are tabulated in table 3. This table shows that a man weighing 65 Kg contains over 40.9 liters of water and that a cat weighing 2 Kg contains over 1.28 liters, which is distributed to the various organs as shown in table 5.

Examination of tables 3 and 4 shows that nearly half of the water in the body is in the muscle, the most active and most frequently used tissue of the body. The skin contains about one fifth of the water in the body. The great importance of evaporation of water from the skin in maintaining a constant body temperature must be remembered. Although the blood mass represents but 5 per cent of the body weight, it is 82 per cent water and occupies third place among the tissues in water content. It contains, then, in a man weighing 65 Kg, approximately 2.65 liters of water as compared to the .37 to .38 liters of water found in the other tissues.

The water of the blood is not distributed equally between the corpuscles and plasma, which make up from 40 to 60 per cent of whole blood, respectively. I have found plasma to be approximately 92 per cent water and corpuscles 68 per cent.

In table 3 it is seen that a man weighing 65 Kg has about 3,195 Gm of blood, of which 2,651 Gm is water. Of this whole blood, 1,533.6 Gm are corpuscles, and 1,661.4 Gm are plasma. From these figures, I find that the corpuscles contain 869.04 Gm, or 33 per cent, of the water in the blood. The plasma contains 1,763.64 Gm or 67 per cent.

It is this 1.76 liters that gives the blood its fluid consistency and enables it to serve its important function of supplying food, oxygen, and other necessities (internal secretions, hormones and enzymes) to the tissue of the body, and of relieving the other 38 liters of waste material to transport it to the proper localities for its discharge from the body.

It is interesting to note in table 4 that the body water in the different species is distributed similarly to that in man.

PREVIOUS WORK ON WATER DEPOTS OF THE BODY

It is known that after a hemorrhage, water is drawn from the tissues into the blood stream, and that salt solutions injected into the blood stream disappear rapidly.

Although these facts concerning hemorrhage and intravenous injection of salt solution have long been known, no one has made an attempt to determine where the fluid comes from in hemorrhage, and only Engles

has attempted to show to what tissues it goes in the case of injected salt solution. He found that following intravenous injection of physiologic sodium chloride solution, all the tissues except bone became "watery." The muscles, skin and kidneys take up the greater proportion, increasing their percentage amount of water 3.86, 3.23 and 3.83 per cent, respectively. The muscles representing 40 per cent of the body weight take up more than two thirds of any added water, but continue to act normally in spite of the added moisture.

TABLE 4—*Percentages of Entire Amount of Water in Body Held by Various Tissues as Computed from Values Given in Table 3*

Organs	Man	Rat	Dog	Cat	Rabbit
Skin	20.6	21.2	14.4	14.8	13.7
Muscle	43.4	51.9	47.9	52.6	56.9
Skeleton	5.5	6.9	8.3	6.4	3.7
Brain	2.3	0.56	1.56	1.59	0.63
Spinal cord		0.001			0.18
Liver	2.4	4.72	4.03	3.2	5.72
Heart	0.58	0.4	0.96	0.45	1
Lungs	0.86	0.66	1.05	0.81	1.39
Kidneys	0.48	0.92	0.75	0.43	0.81
Spleen	0.21	0.3	0.26	0.34	0.11
Blood	6.47	6.8	8.82	6.02	8.12
Intestine	2.14	4.63	7.45	5.63	4.35
Rest of body	14.86	1.11	4.44	8.64	3.15

TABLE 5—*Liters of Water Distributed in the Various Organs in a Man Weighing 65 Kg. and in a Cat Weighing 2 Kg.*

Organs	Man	Cat
Muscle	17.7	0.6
Skin	8.4	0.1
Blood	2.65	0.07
Skeleton	2.27	0.08
Liver	1	0.04
Brain and cord	0.97	0.02
Intestine	0.87	0.05
Lungs	0.35	0.01
Heart	0.24	0.005
Kidneys	0.19	0.005
Spleen	0.08	0.004

In his work, Engles used dogs in series. On one series he made determinations of normal water content, on another, of the water content of the tissues after intravenous injection of physiologic sodium chloride solution. Since muscle constitutes 40 per cent of the body weight and takes up more than two thirds of any added water, he assigns to muscle the greatest importance as water depot.

MY EXPERIMENTS

In my experiments I have determined the water content of a few of the most important tissues before and after altering the water supply on the same animal, in an attempt to show from what tissues most of the water comes after a hemorrhage and to what tissue it goes when injected as salt solutions.

The experiments were carried out on cats in the following manner

1 Preliminary experimental care of the animal was disregarded except in the first series, in which the alteration of the water balance was effected by hemorrhage. The animals had had (a) no previous experimental care, (b) no food or fluid for thirty hours previous to the experiment and (c) only water for five days

2 The cats were anesthetized with ether and their weight was recorded

3 The hair was clipped closely and evenly from the legs, abdomen and neck

4 A cannula was put in the carotid artery in order to obtain specimens of blood

5 The abdominal wall was opened, but closed immediately with hemostats in order to prevent the loss of water by evaporation

6 The gastrocnemius muscle was exposed, and the opening was closed with a hemostat in order to prevent the muscle from losing water by evaporation

7 The animal was prepared so that all specimens could be taken almost instantaneously. Two samples of each tissue (skin, muscle, spleen, intestine, liver and blood) were placed in weighing bottles that had been accurately weighed. Two samples of each tissue were taken for the purpose of having a check

8 A sample of blood (2 cc) for hemoglobin was collected in a small bottle containing a few crystals of potassium oxalate

9 The kidneys were tied off in order to decrease the loss of water from the body

10 Alteration of the water balance was made by one of the following procedures

(a) Hemorrhage, 15 cc per kilogram of body weight

(b) Intravenous injection of distilled water, 25 cc per kilogram

(c) Intravenous injection of 0.45 per cent sodium chloride, 20 cc per kilogram

(d) Intravenous injection of 0.9 per cent sodium chloride, 20 cc per kilogram

(e) Intravenous injection of 1.8 per cent sodium chloride, 20 cc per kilogram

(f) Intravenous injection of 0.6 per cent calcium chloride, 20 cc per kilogram

(g) Intravenous injection of 1.2 per cent calcium chloride, 20 cc per kilogram

(h) Intravenous injection of 2.4 per cent calcium chloride, 20 cc per kilogram

11 Thirty minutes were allowed for an effect to take place. All incisions were kept closed with hemostats, and the body was covered with a sheet

12 Samples of tissue were clipped from as nearly the corresponding place on the other side of the body as possible. Two samples were also taken here for a check

13 The samples were weighed and put in an electric oven at from 102 to 104 C until the weight became constant

14 After cooling the samples in a desiccator over sulphuric acid, the weight was taken, and the percentage of water in each sample was calculated

The method used in making determinations of hemoglobin consisted in taking the sample of blood collected before the water balance was altered as 100 per cent. The second sample, taken thirty minutes after the water balance was altered, was compared with the normal in a colorimeter. The three-way tap pipet described by Scott¹ was used to insure exactly the same amount of blood in each case

The technic was so developed by experience that I was able to obtain samples of each type of tissue varying not more than 0.04 Gm in weight. My next difficulty was to consider the blood content of these tissues

Naturally, the blood content of these tissues would greatly alter my determinations of water. To overcome this difficulty, I cut the sample in pieces and allowed the blood exuding from each piece to be absorbed by paper toweling. Each sample was treated in exactly the same manner to the minutest detail

1 Scott, F. H. Factors Influencing the Interchange of Fluid Between Blood and Tissue Spaces. I. Blood Pressure, *Am J Physiol* **44** 298, 1917

TABLE 6—Percentage of Water Contained in the Various Organs Before and After Hemorrhage

Cat	Weight in Kg	Skin		Muscle		Spleen		Liver		Intestine		Blood	
		Organ Weight, Gm	Before After	Organ Weight, Gm	Before After	Organ Weight, Gm	Before After	Organ Weight, Gm	Before After	Organ Weight, Gm	Before After	Organ Weight, Gm	Before After
1	1.63	227.2	69.2 68	739.8	77.4 76.8	4.5	78.8 78	48.24	76.7 74.7	61.9	78.9 77.1	72.6	81.1 85.7
2	2	278.8	61.9 60.7	907.2	78.9 78.5	5.6	79.7 79.2	59.20	75.8 74.1	76	78.2 77.1	89.2	83.1 89.5
3	2.5	348.5	67.3 64.1	1,131	75.6 75.2	7	78.6 78.1	74	77 73.9	95	77.3 76.4	111.5	80.2 82.2
4	2.1	292.7	67.6 63.6	952.5	74.9 74.5	5.8	78.7 78.1	62.16	78.2 75	79.8	79 78.4	93.6	81 82
5	1.5	209.1	66.2 63.3	680.4	77.2 76.3	4.2	79.1 78.7	44.4	76.2 73.1	57	78.3 76.6	66.9	81 82.5

	Extent of Hemorrhage in Cc	Percentage of Hemoglobin After Hemorrhage
1	30	66
2	30	78
3	40	83
4	40	80
5	30	85

TABLE 7—Computations Made from Table 6 on the Water Content of Various Organs Before and After Hemorrhage

Cat*	Skin		Muscle		Spleen		Liver		Intestine		Blood	
	B	A	G D	B	A	G D	B	A	G D	B	A	G W L T %
1	157.2	151.1	—2.8	572.6	568.1	—4.5	3.59	3.55	—0.04	48.87	47.72	30.1 9.49 31.5
2	172.5	169.2	—3.3	697.6	694	—3.6	4.46	4.43	—0.03	59.40	58.1	25.9 6.63 25
3	234.5	233.3	—1.2	837.3	832.7	—4.6	5.50	5.40	—0.10	73.10	72.5	28.8 19.20 66
4	197.8	186.1	—11.7	713.4	709.6	—3.8	4.60	4.50	—0.1	63	62.5	23.8 18.10 76
5	138.4	134.4	—4	525.2	519.1	—6.1	3.32	3.31	—0.01	41.60	43.6	13.5 12.5 92

B indicates grams of water in the organ before hemorrhage, A, grams of water in the organ after hemorrhage, G D, grams of water taken up or lost by organ, L, taken up by tissue, —, lost to tissue, G W, grams of water gained by blood, L T, total grams of water given up by tissues %, percentage of fluid entering the blood stream found to be coming from the tissues examined

* Cats 1 and 2 were normal from the stockroom (typical of ten such experiments), cats 3 and 4 had no food or fluid for thirty two and seventy two hours, respectively (typical of six such experiments), cat 5 had only water for five days (typical of four such experiments)

The next difficulty to overcome was that of obtaining dry tissue. Because it is so highly hygroscopic, Benedict expressed his doubt, in a personal conversation, as to whether any one had ever obtained dry tissue. I dried a few samples of tissue in an electric oven from 102 to 104 C over a period of from twenty-four to thirty-six hours.

Samples of muscle weighing 0.183 Gm immediately after removing from the oven increased in weight by 0.024 Gm or 24 mg when exposed to the air for five minutes. When exposed in a desiccator for the same length of time, a sample of muscle weighing 0.2 Gm increased its weight by 0.016 Gm or 16 mg. Other samples dried in the oven at the same temperature and over the same time did not gain in weight if the stopper was placed on the weighing bottle before removing it from the oven. Some of these samples were exposed in the air and others were left in the desiccator for a week without undergoing any noticeable change.

Believing these difficulties to be overcome, I proceeded with the control experiments, which consisted of carrying out the experimental procedure as just outlined, eliminating only the factor altering the water balance. Results from a series of five control experiments show that the percentage of water in the tissues examined did not vary more than 0.2 of 1 per cent at the most in any case. I considered 0.3 per cent as the limit of error.

After establishing the reliability of my procedure and methods, I proceeded with the experimental work, the results of which are shown in the accompanying tables, those for hemorrhage are given in detail to show the type of data used, those for the injections of watery solutions are summarized in table 10.

COMMENT

Table 7 shows that severe hemorrhage resulted in the blood becoming more "watery," while the other tissues of the body lost water. This result was true whether the animal was starved, given only water or taken direct from stock before the experiment.

Tables 8 and 9 show the average results. Although the greatest amount of water entering the blood stream after hemorrhage in normal cats from stock (cats 1 and 2) comes from the muscles, they lost the least amount (0.5 Gm) of water for each hundred grams of tissue. This is also true of the results obtained with cat 5 (water only for five days). In this case 45.2 per cent of the water entering the blood stream came from the muscles at the rate of 0.9 Gm for each hundred grams of tissue. In these same experiments, the next greatest amount (11 per cent) of water came from the skin. The liver contributed approximately the same percentage (3.5 per cent) as the intestine (3.6 per cent) in cats 1 and 2, but gave a much larger quantity in the experiment with cat 5.

Further study of these experiments shows that for each hundred grams of tissue the liver lost the greatest amount of water (21.32 Gm), while the intestine and the skin lost approximately the same amount (16 and 12 Gm)

These results bear an analogy with Starling's² interpretation of the relative permeability of capillaries in different parts of the body. He found that lymph from muscles of the limbs was from 2 to 4 per cent protein, that from the intestine, from 4 to 6 per cent, that from the liver, from 6 to 8 per cent. From this he deduced that the capillaries of the liver were the most permeable, those of the intestine next and those of the muscle the least. This parallels the results already mentioned,

TABLE 8—*Source of Fluid Entering Blood Stream Expressed in Percentage of Amount Coming from Various Tissues*

	Cat	Skin	Muscle	Liver	Intestine	Spleen
1		9.3	14.9	3.3	3.4	0.13
2		12.7	14	3.8	3.8	0.03
Average		11	14.45	3.5	3.6	0.08
3		38	16	8.3	3.1	0.34
4		49	16	8.4	2.1	0.42
Average		43.5	16	8.35	2.6	0.07
5		30	45.2	10.4	0.74	0.72

TABLE 9—*Amount of Fluid Given Up by 100 Gm of Tissue Following Hemorrhage Computed from Table 6*

	Cat	Skin	Muscle	Liver	Intestine	Spleen
1		1.2	0.6	2.2	1.9	1
2		1.2	0.4	2	1.3	0.6
Average		1.2	0.5	2.1	1.6	0.8
3		3.2	0.4	3.2	0.9	3.3
4		4	0.39	3.2	0.7	2.17
Average		3.6	0.4	3.2	0.8	2.73
5		2.1	0.9	3.2	1.75	0.25

that is, that muscle, with the least permeable capillaries, lost the least water per unit mass of tissue, and that the liver, with the most permeable, lost the most per unit mass.

An average of the results from cats 3 and 4 (no food or fluid for thirty-two and seventy-two hours, respectively) shows that the skin contributed not only the greatest amount (3.6 Gm) for each hundred grams of tissue, but also a greater percentage (43.4 per cent) of the fluid entering the blood stream than any of the other tissues. This was not only an increase over the amount lost for each unit mass of tissue in cats 1 and 2, but also an increase in the percentage of water it contributed toward that entering the blood stream.

The next greatest percentage (16 per cent) came from the muscles, but at the rate of only 0.4 Gm per hundred grams of tissue. This was

² Starling, E. H. The Influence of Mechanical Factors on Lymph Production, *J. Physiol.* **16**: 224, 1894.

TABLE 10—Changes in the Water Content in Various Organs Following Intravenous Injection of Watery Solutions

	Distilled Water		0.45% Sodium Chloride		0.9% Sodium Chloride		1.8% Sodium Chloride		0.6% Calcium Chloride		1.2% Calcium Chloride		2.4% Calcium Chloride	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Blood	23.7	17	37.26	20	19.15	27.7	39.3	33.7	61.1	36.1	71.5	41.8	100+	
Muscle	13.1	0.75	21.70	1.3	0	0	10.8	-1.2	16.1	1.1	Loss	-1.3	Loss	-0.5
Liver	9.5	7.6	5.57	1.6	3.91	1.3	3.15	1.1	5	3.0	3.2	2.4	Loss	-2
Skin	5.8	1.1	11.1	1.9	13.37	1.5	17.5	1.8	8.1	1.11	Loss	-3.55	Loss	-1.2
Intestine	2.7	2.1	4.5	2.8	2.21	1.9	2.81	1.9	2.6	1.33	3.9	2.6	Loss	-0.6
Spleen	0.16	1.6	0.09	0.9	0.07	0.9	0.09	0.9	0.18	0.87	0.26	2.4	0	0

Under A are listed the percentage of the injected fluid remaining in the blood stream or absorbed by the various tissues at the end of thirty minutes, under B, the grams of fluid taken up or lost (—) by 100 Gm of tissue.

The results with distilled water are an average of six experiments with 0.15% sodium chloride, 8, 0.9% sodium chloride, 8, 1.8% sodium chloride, 6, 0.6% calcium chloride, 6, 1.2% calcium chloride, 6, 2.4% calcium chloride, 1.

by far the least amount of water lost per unit mass by any tissue in these experiments

Of the total amount of fluid entering the blood stream, 8.35 per cent came from the liver at the rate of 3.2 Gm per hundred grams of tissue. This was an increase of 1 Gm of water for each hundred grams of tissue over the results with cats 1 and 2. It is nearly as much as for each unit mass of skin, and half as much as for each unit mass of muscle. Here one must recall that there is approximately fifteen times as much muscle as liver in the cat, and yet muscle lost only twice as much water as the liver.

The intestine ranks fourth in regard to the amount (2.6 per cent) of water that came from it after the hemorrhage. For each hundred grams of tissue it lost 0.8 Gm of water, being 0.3 of a Gm more than that lost by muscle.

For each hundred grams of its tissue the spleen lost 2.73 Gm of water, but because of its size, only 0.07 per cent of the fluid that entered the blood came from it.

Examination of table 10 shows that distilled water leaves the blood stream more rapidly than any of the other solutions. Solutions having a higher salt content left the blood more slowly, and the increase in water content shown by the tissues decreased. With isotonic sodium chloride there was no change in the water content of muscle, but there was a decrease in its water content thirty minutes after the injection of hypertonic sodium chloride. Following the injections of hypotonic calcium chloride, the tissues did not show as big an increase in their water content as they did when hypotonic sodium chloride was injected. With the exception of muscle, the tissues did not become as "watery" as they did after the injection of isotonic or even of hypertonic sodium chloride. There was also a greater percentage of the injected solution remaining in the blood stream at the end of thirty minutes than there was when hypertonic sodium chloride was injected.

Only 2.6 per cent of the isotonic calcium chloride solution injected had left the blood stream at the end of thirty minutes. Muscle and skin both showed a decrease in their water content after its injection.

Following the injection of a 2.4 per cent solution of calcium chloride, there was more water (above normal amount) in the blood stream at the end of thirty minutes than had been injected. The principal source for this water was the skin, and the next most important source was the muscle, some came from the intestine, but little came from the spleen.

Following the injection of distilled water or the hypotonic salt solutions, the increase in the water content of the tissues as expressed in grams of water taken up by 100 Gm of tissue is parallel to Starling's interpretation of the permeability of the capillaries in those regions. The liver showed the greatest increase for each hundred grams of its

tissue, while the muscle showed the least. It is worthy of note, however, that muscle took up a larger percentage of the water added per se than any other tissue. Liver took up the next greatest amount, skin, the third greatest amount, the intestine, the fourth largest amount and spleen the least.

This was relatively true when hypotonic salt solutions were injected, except that skin not only showed an increase of more per unit mass of tissue than it did with distilled water, but it also absorbed a greater percentage of the injected fluid than did the liver. When isotonic sodium chloride was injected, the skin not only showed an increase of more water per unit mass of tissue than it did following the injection of the hypotonic solution, but also contained a greater percentage of the fluid injected than any other tissue. Likewise, following the injection of a hypertonic sodium chloride solution, the skin showed a still greater increase in water content per unit mass of tissue than it did with isotonic sodium chloride, there was also an increase in the percentage amount of the injected fluid that it had taken up.

The injection of isotonic sodium chloride solution did not result in an alteration of the water content of muscle, but after the injection of a hypertonic solution there was a diminution in its water content.

This result differs from that of Engles,³ who found that muscle increased its water content by 3.86 per cent following the injection of physiologic sodium chloride. His work was carried out on dogs in series and not as a complete experiment on one animal.

In his work on the significance of the tissues as a depository for chlorine, Wahlgren⁴ found that the muscles not only had the lowest percentage of chlorine content, but also increased their percentage amount the least when chlorine was given intravenously in the form of sodium chloride. He also found that water passed from the muscles into the blood after intravenous infusion of hypertonic sodium chloride solutions.

The results of Tashiro,⁵ who observed the effect of injecting hypotonic and hypertonic saline on the water content of striated muscle of rabbits obtained the same results as I did on that tissue.

Injection of 1.2 per cent calcium chloride resulted in a marked decrease in the water content of the skin and muscle, but in an increase in the water content of the liver, intestine and spleen. The muscle lost more (4.3 Gm.) for each hundred grams of its tissue than the skin. The

³ Engles, W. Die Bedeutung der Gewebe als Wasserdepots, Arch f exper Path u Pharmacol **51** 346, 1904.

⁴ Wahlgren, V. Ueber die Bedeutung der Gewebe als Chlordepots, Arch exper Path u Pharmacol **61** 97 (Sept 30) 1909.

⁵ Tashiro, N. Changes in Water Content of Striated Muscles Caused by Disturbances of Water Metabolism of Rabbits, Arch f exper Path u Pharmacol **3** 218, 1926.

intestine showed an increase of 2.6 Gm of water for each hundred grams of tissue as compared to 2.4 Gm for each hundred grams of tissue in the liver and in the spleen

There was a marked depletion in the water content of all the tissues following the injection of 2.4 per cent calcium chloride solution. The effects of this injection parallel those observed after severe hemorrhage. The blood became more "watery" than could be accounted for by the fluid injected, and all tissues lost water. The muscle lost the least per unit mass of tissue and, with the exception of skin, the liver lost the most.

SUMMARY AND CONCLUSIONS

1. The distribution of water in man and in the rat, dog, cat and rabbit given in table 4 shows that approximately half of the body water is in the muscles. The skin contains about one fifth of the water in the body, and the blood about 7 per cent. Of the water in the blood, 67 per cent is in the plasma and 33 per cent is in the corpuscles.

2. All the tissues lost water after hemorrhage. The amount of water entering the blood came from the organs in the following order (tables 8 and 9):

A In cats having a normal supply of water in their tissues: (1) muscle, 14.45 per cent, skin, 11 per cent, intestine, 3.6 per cent, liver, 3.5 per cent, spleen, 0.08 per cent. (2) Per hundred grams of tissue, the order was as follows: liver, 2.1 Gm, intestine, 1.6 Gm, skin, 1.2 Gm, spleen, 0.8 Gm, muscle, 0.5 Gm.

B In cats that had been deprived of water and food for five days: (1) skin, 43.5 per cent, muscle, 16 per cent, liver, 8.35 per cent, intestine, 2.6 per cent, spleen, 0.07 per cent. (2) Per hundred grams of tissue: skin, 3.6 Gm, liver, 3.2 Gm, spleen, 2.73 Gm, intestine, 0.8 Gm, muscle, 0.4 Gm.

3. Following the injection of distilled water or hypotonic salt solutions, the fluid leaving the blood stream at the end of thirty minutes was distributed to the tissues in the following order (table 10): (1) muscle, 13-21 per cent, liver, 9.5-5.5 per cent, skin, 5.8-11 per cent, intestine, 2.7-4.5 per cent, spleen, 0.1-0.8 per cent. (2) Per hundred grams of tissue, the amount added was as follows: liver, 7.6-3 Gm, intestine, 2.1-1.3 Gm, spleen, 1.6-0.8 Gm, skin, 1.1-1.9 Gm, muscle, 0.7-1.1 Gm.

4. Following the injection of isotonic and hypertonic sodium chloride solutions all tissues, except muscles, showed an increase in their water content.

A After isotonic sodium chloride, there was no change in the water content of muscle, while there was a decrease in its content after hypertonic sodium chloride was injected.

B The skin showed a greater increase in its water content the greater the sodium chloride content of the injected solution. Its increase per unit mass of tissue was least after distilled water and greatest after hypertonic sodium chloride was injected.

5 Following the injection of 1.2 per cent calcium chloride solutions, the muscle and skin showed a decrease in their water content. Muscle showed the greatest difference per unit mass of tissue. The intestine showed an increase of 2.6 Gm. of tissue as compared to 2.4 Gm. for each hundred grams of tissue in the liver and of the spleen.

6 The results after injecting 2.4 per cent calcium chloride were parallel to those after hemorrhage.

7 Although the muscle contains nearly one half of the body water, and loses the least per unit mass of tissue, it gives up more fluid than any other tissue when the animal is deprived of fluid, and takes up by far the greatest portion of any water added as water per se or as a hypotonic salt solution. It would seem justifiable, therefore, to indicate muscle as the most important water reserve of the body, it stores the greatest quantity of any excess, and acts as a safeguard against the loss of too much water from the body.

8 The importance of skin as a reserve to take care of any excess fluid, especially when added as a sodium chloride solution, must not be overlooked. The experience with partially dehydrated animals indicates that skin will furnish the greatest quantity of water to the body if a further dehydration should occur.

9 The liver and the intestine appear to respond more quickly than any other tissues when there is an alteration in the water content of the body.

10 The promptness and the degree of reaction of the various tissues examined to any alteration in the fluid content of the body bear a relation to Starling's interpretation of capillary permeability. This is particularly true in the case of hemorrhage, or when distilled water or hypotonic salt solutions are injected.

RELATIVE HYPOTENSION OF FOREIGNERS IN CHINA *

C L TUNG, M D
PEKING, CHINA

It has been the common experience in studying groups of healthy Chinese to find that the blood pressure, both systolic and diastolic, is lower than that in occidental races. Table 1 summarizes the results of several investigations.

In the West, with special reference to the United States, Alvarez ¹ found that the average systolic blood pressure of 6,000 healthy men, ranging in age from 16 to 40 years, was 129 millimeters of mercury and in women 117. From a group of 141,840 persons of both sexes, ranging in age from 20 to 44 years, Symonds ² obtained an average systolic blood pressure of 125 and a diastolic pressure of from 80 to 84. According to

TABLE 1—*Records of Blood Pressure of Chinese Men*

Author	Locality	Number of Subjects	Age	Average Systolic Pressure, Mm Hg	Average Diastolic Pressure, Mm Hg
Kao (Nat M J China S 101, 1922)	Hunan (Central China)	63	21 to 25	116	71
Kao (Nat M J China S 101, 1922)	Hunan (Central China)	10	26 to 42	113	71
Cidbury (China M J 37 823, 1923)	Canton (South China)	700	15 to 30	101	65
Kilborn (China M J 10 1, 1926)	Szechuan (West China)	741	14 to 31	111	70
Ying (China M J 10 641 1926)	Shaoshing (East China)	182	21 to 50	113	72

the available evidence, therefore, the average systolic pressure of healthy adults in the United States is approximately 125 and the diastolic 80, with slightly lower figures (from 5 to 10 lower) for women, while the average systolic pressure of Chinese is about from 110 to 115 and the diastolic about 70.

Although both the systolic and the diastolic blood pressure of the Chinese is known to be about 10 lower than that of westerners, little study has been made of the effect of residence in the Orient on the blood pressure of westerners. Musgrave and Sison ³ were the first to point out an apparent lowering of blood pressure following residence in the Philippines for from one to ten years or more. Their figures, based on the blood pressure of ninety-seven foreigners (varying in age from

* From the Department of Medicine, Peking Union Medical College.

1 Alvarez, W. C., Wulzen, R., and Mahoney, L. J. Blood Pressure in 15,000 University Freshmen, Arch Int Med **32** 17 (July) 1923.

2 Symonds, B. The Blood Pressure of Healthy Men and Women, J A M A **80** 232 (Jan 27) 1923.

3 Musgrave and Sison. Philippine J Sc, Sec B **5** 325, 1910.

25 to 40), most of whom were Americans in the Philippine Civil Service and the United States Army, were as given in table 2 (Erlanger instrument used)

The figures for ten French Sisters of Charity (from 24 to 38 years), were as given in table 3

These figures show that apparently there is a progressive decrease in blood pressure accompanying prolonged sojourn in the tropics

In 1911, Chamberlain⁴ found that the average systolic pressure of 992 American soldiers serving in the Philippines (average age, 26) was 115. The average length of their term in this service was about eleven months. This figure coincided with the average systolic pressure of 115 in 386 Filipinos whose average age was 25 years. Chamberlain concluded that for neither race is the blood pressure materially below the

TABLE 2—*Average Blood Pressure of Foreigners in the Philippine Islands*

Length of Residence	Average Systolic Pressure
1 month to 1 year (65 cases)	124
1 year to 5 years (15 cases)	115
5 years to 10 years (8 cases)	116
Over 10 years (9 cases)	113

TABLE 3—*Average Blood Pressure of Ten French Sisters of Charity*

Length of Residence	Average Systolic Pressure
15 days to 1 year	127
1 year to 5 years	112
Over 5 years	110

figures to be expected for white men residing in the temperate climates. This conclusion may be questioned for two reasons. First, the average systolic pressure of healthy men, aged 26, in the West is about 125, as has just been shown, second, the period of residence in the tropics in this author's cases was probably too short to have any marked effect on the blood pressure. Foster⁵ reported that the blood pressure of foreigners in Changsha was about the same as that of the Chinese, and that the blood pressure of many persons was lower in China than it was in America. He based the latter statement on about thirty records taken both in America and in Changsha.

In table 4 I have compiled the blood pressure readings, systolic and diastolic, of fifty-eight westerners (mostly Americans), members of the staff of the Peking Union Medical College, showing determinations

⁴ Chamberlain. Philippine J. Sc., Sec. B 5:467, 1911.

⁵ Foster. Abstracts of Papers for China Medical Association Conference, Peking, 1926, p. 10.

made at home and in Peking. The age column gives the age of each person at which his blood pressure was first taken. The readings in America or, rarely, in Europe are taken from records of physical examinations made abroad, as indicated, and kept on file here. In about two thirds of the cases, the records in Peking represent those obtained during routine physical examinations performed every two years after the person's arrival in China, or by special appointment for the determination of blood pressure. For the sake of clearness, the results of only the most recent of these examinations are presented in this article. In the other

TABLE 4—*Parallel Records of Blood Pressure of Fifty-Eight Americans in the United States and in China*

Number	Sex	Age	Blood Pressure in the United States		Blood Pressure in China		Change in Blood Pressure	
			Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
1	M	30	135	75	122*	70*	-13	-5
2	M	33	120	80	118	65	0	-15
3	M	32	112	76	110	64	0	-12
4	M	39	120	70	110	60	-10	-10
5	M	35	128	70	110	70	-18	0
6	M	70	118	80	125	75	+7	-5
7	M	44	122	80	110	70	-12	-10
8	M	34	120	76	114	75	-6	0
9	M	29	120	90	110	66	-10	-24
10	M	24	100	70	106	64	+6	-6
11	M	36	115	68	120	60	+5	-8
12	M	32	112	78	100	58	-12	-20
13	M	35	130	80	115	75	-15	-5
14	M	36	110	74	92	58	-18	-16
15	M	44	106	70	112	70	+6	0
16	M	39	135	90	108	66	-27	-24
17	M	25	122	80	108	62	-14	-18
18	M	42	125	80	108	66	-17	-14
19	M	37	145	80	84	60	-61	-20
20	M	52	140	105	108	70	-32	-30
21	M	42	120	84	98	56	-22	-28
22	M	43	125	80	110	70	-15	-10
23	M	21	100	60	90	60	-10	0
24	M	22	110	70	138	80	+20	+10
25	M	28	124	82	138	90	+14	+8
26	M	26	110	65	108	64	0	0
27	M	38	100	60	112	72	+12	+12
28	M	28	110	75	102	58	-8	-17
29	F	31	110	80	108	60	0	-20
30	F	40	132	80	110	68	-22	-12
31	F	36	120	80	100	60	-20	-20
32	F	36	104	64	104†	60†	0	0
33	F	33	120	65	110	90	-10	+25
34	F	28	120	80	110	65	-10	-15
35	F	39	118	70	120	70	0	0
36	F	33	115	75	110	58	-5	-17
37	F	30	105	75	100	50	-5	-25
38	F	33	115	60	112	70	0	+10
39	F	28	118	84	109	62	-9	-22
40	F	30	130	80	110	68	-20	-12
41	F	16	108	60	105	65	0	+5
42	F	28	100	55	110	55	+10	0
43	F	26	118	82	90	60	-28	-22
44	F	32	115	70	112	65	0	-5
45	F	34	112	80	106†	66†	-6	-14
46	F	32	124	80	102	72	-22	-8
47	F	35	120	76	100	65	-20	-11
48	F	42	121	70	114	78	-7	+8
49	F	28	130	90	110	60	-20	-30
50	F	25?	118	85	118	68	0	-17
51	F	36	106	68	120	60	0	-8
52	F	45	120	75	98	66	-22	-9
53	F	29	125	95	114	60	-11	-35
54	F	33	110	60	110†	40†	0	-20
55	F	29	115	85	95	54	-20	-31
56	F	28	115	80	95	60	-20	-20
57	F	51	120	80	130	78	+10	0
58	F	36	130	90	110	70	-20	-20

* Blood pressure in China during diarrhea

† Blood pressure in China during pregnancy

third of the cases the readings are taken from histories of patients who have called at the office on account of minor ailments, or from hospital histories. Care has been exercised to exclude readings taken while the patients had diarrhea, dysentery, acute respiratory infections, prolonged fever or illness of any kind, or when patients were pregnant, except in a few cases designated in the column under "Notes."

The average age in the foreign group reported was 34. The time at which the Peking reading was taken is not indicated, because in many cases an average of the readings of different years is presented (in hospital cases), but the average time was from two and one-half to three years after the reading taken abroad. No Peking figure was taken within one year after the person's arrival in China, except in case 8 of the foreign group and in case 3 of the Chinese group, both being obtained within two months after the subject's arrival in China.

In regard to the technic of blood pressure reading, I do not know how the blood pressure in America was taken, in China, it was taken by several different physicians. The apparatus used was a mercury manometer. About half of the blood pressures were taken when the

TABLE 5—*Grouping of Blood Pressure of Fifty-Eight Americans in the United States and in China*

Systolic pressure	80-89	90-99	100-109	110-119	120-129	130-139	140-149
United States	0	0	9	20	20	7	2
China	1	7	16	25	4	3	0
Diastolic pressure	40-49	50-59	60-69	70-79	80-89	90-99	100-109
United States	0	1	10	18	23	5	1
China	1	8	30	16	1	2	0

subjects were in a supine position and half when they were seated. The auscultatory method was used, and the first appearance of a sharp thumping sound was recorded as the systolic pressure, the sudden change from a sharp tap to a dull, feeble thud was regarded as the diastolic pressure.

In the column under "Changes in Blood Pressure," an increase of 5 or more is indicated by a plus sign and a decrease of 5 or more by a minus sign. No change (a change of 4 or less is considered as no change) is signified by "0."

Table 5 shows the grouping of the records of the blood pressure of this group in the United States and in Peking, and no further comment is necessary.

As will be seen from table 6, the average systolic pressure of fifty-eight foreigners in America is 118 and the average diastolic, 76, while the average systolic pressure in Peking is 109 and the average diastolic, 65, although the subjects have increased in average age from about 34 to 37. There is an average lowering of 9 in the systolic, and of 11 in

the diastolic pressure. Thus it appears that there is a distinct tendency for the blood pressure of foreigners resident in China to approach that of the Chinese.

Analyzed from the point of view of percentage of increase or decrease in blood pressure, it is seen from the results in table 6 that the systolic pressure shows a decrease in 64 per cent, and an increase in only 15 per cent in China. The diastolic pressure is even more striking, with 72 per cent showing a fall in pressure and only 12 per cent a rise.

COMMENT

Although this series is too small to afford a basis for any far-reaching conclusions, it indicates that there is a fall in blood pressure, both systolic and diastolic, in the majority of foreigners who take up their residence in China for any length of time. Musgrave and Sison² thought that the decrease in blood pressure was due to a lower peripheral resistance, associated with increased secretory activity of the sweat glands. Gastro-intestinal disturbances were also suggested by these authors as capable

TABLE 6—*Average Blood Pressure in the United States and in China, and Percentage of Observations Showing Changes*

	Fifty Eight Americans	
	Systolic	Diastolic
United States	118	76
China	109	65
No change	21 per cent	16 per cent
Increase	15 per cent	12 per cent
Decrease	64 per cent	72 per cent

of producing motor disturbances, principally through the portal circulation and the splanchnic tone. It is claimed by Huggard⁶ that the low blood pressure in persons who reside in the tropics is associated with dilatation of the peripheral blood vessels, as well as with increased elasticity of the vessel wall.

While the low blood pressure of the Chinese may be due in small part to a diet less rich in meat, the diet of foreigners is not essentially different from that in America. The perpetual rush, tension and excitement that characterize American life and the comparatively slower and calmer life in Peking, although the work here may be no less strenuous, may be important factors in the causation of the relative hypotension. In a recent physiologic review,⁷ MacWilliam says: "The pronounced effects of mental stress, excitement and worry in producing and maintaining high blood pressure emphasize the significance of the nervous system

6 Huggard, quoted in Castellani and Chalmers. *Manual of Tropical Medicine*, ed. 2, 1913, p. 89.

7 MacWilliam. *Physiol. Rev.* 5: 303, 1925.

whether exercised indirectly through the cardiovascular innervation or more directly through endocrine or metabolic alterations" Lombard⁸ and Krogh⁹ emphasize the independent contractility of the capillaries and arterioles. Studies on the vasomotor condition in the tropics and in the Orient are lacking at present.

It is true that there is increased sweating in the tropics, but there is no definite knowledge of the relation of sweating to vasomotor states. Evidently there may be a cutaneous vasodilatation associated with sweating, as may be seen during flushing caused by excitement or embarrassment, but there may be also a state of pallor with sweating, as that occurring during fright. In any case this mechanism does not explain the hypotension reported here, since Peking is neither tropical nor subtropical. It is a point of interest that hypertension, which has been considered as bearing a special relation to tropical residence, is also present in the temperate zone.

MacWilliam⁷ has epitomized the present knowledge of hypotension.

But in persistent low pressure attendant on exhausting diseases or occurring without obvious cause (essential hypotension) the available data are, as in the case of persistent high pressure, inadequate for satisfactory explanation of the mechanism involved—whether a defective peripheral resistance or defective cardiac output depending, apart from cardiac enfeeblement, on lessened return of blood to the heart as a result of undue expansion of the capacity of the vascular system from capillary or venous relaxation, contraction of venules, diminished volume of blood in circulation, etc. It is also unknown how far such conditions are mediated through the nervous system and how far due to the direct influence of chemical agents—depressor bodies, lack of pressor substances, etc.

What true significance the relative hypotension of the westerners in China and in the tropics has remains to be seen.

SUMMARY

1 An analysis of parallel records of the systolic and the diastolic blood pressure of fifty-eight Americans at home and in Peking about three years later shows an increase of systolic pressure in 15 per cent of the subjects, no change in 21 per cent and a decrease in 64 per cent. The diastolic pressure shows an increase in 12 per cent, no change in 16 per cent and a decrease in 72 per cent.

2 The average systolic pressure of fifty-eight Americans in America is 118 millimeters of mercury and in China 109. The average diastolic pressure in America is 76, while it is only 65 in Peking. Thus, there is an average decrease of 9 in systolic pressure in Peking and an average decrease of 11 in diastolic pressure.

8 Lombard. *Am J Physiol* **24** 335, 1912.

9 Krogh. *Anatomy and Physiology of the Capillaries*, 1922, p. 23.

DISEASES OF THE LIVER

VI A COMPARATIVE STUDY OF CERTAIN TESTS FOR HEPATIC FUNCTION IN CASES OF CIRRHOSIS OF THE LIVER *

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During the last three years we have been engaged in an attempt to evaluate the clinical usefulness of certain tests for hepatic function. In previous communications we have reported the results of various aspects of this study.¹ At present we wish to report on the functional changes observed in patients with cirrhosis of the liver.

Of a group of more than 100 cases originally diagnosed cirrhosis of the liver, the history and physical observations were characteristic and the diagnosis apparently unmistakable in the fifty cases selected for this report. In the majority the diagnosis was confirmed by examination of the liver at operation or necropsy. Syphilis was excluded in these cases by the history and physical examination and by serologic tests. Observations made in the cases of cirrhosis associated with splenic anemia (so-called Banti's disease) and with hemolytic jaundice have previously been reported.

The presentation of this material has proved singularly difficult because of the present confusion with regard to the classification of cirrhosis. While textbooks of medicine recognize certain types of cirrhosis and make clear-cut distinctions along clinical, etiologic or pathologic lines, any one observing and studying such cases in any number quickly recognizes the great variation in clinical types, and appreciates how incomplete and unsatisfactory is the present knowledge of hepatic disease. Epplen² has recently pointed out the confused and unsatisfactory

* From the Division of Medicine, Mayo Clinic and the Mayo Foundation.

1 Greene, C H, Snell, A M, and Walters, W. Diseases of the Liver. I. A Survey of Tests of Hepatic Function, Arch Int Med **36** 248 (Aug) 1925. Greene, C H, McVicar, C S, Rowntree, L G, and Walters, W. Diseases of the Liver. III. A Comparative Study of Certain Tests for Hepatic Function in Patients with Obstructive Jaundice, Arch Int Med **36** 418 (Sept) 1925, Diseases of the Liver. IV. Functional Tests in Cases of Carcinoma of the Liver and Biliary Tract, Arch Int Med **36** 542 (Oct) 1925. Greene, C H, and Conner, H M. Diseases of the Liver. V. A Comparative Study of Tests of Hepatic Function in Certain Diseases of the Hematopoietic System, Arch Int Med **38** 167 (Aug) 1926.

2 Epplen, F. The Pathology of Cirrhosis of the Liver, An Historical-Pathologic Study, Arch Int Med **29** 482 (April) 1922.

nature of the various attempts at classification on an etiologic or pathologic basis. We have felt that an attempt at the reclassification of the cirrhoses at the present time would be premature, of questionable value, and would involve considerable presumption on our part. Nevertheless, presentation of the functional studies demands some recognition of the various types of cases. Therefore we have adopted the following grouping for this purpose.

Portal cirrhosis or ascitic cirrhosis (cirrhosis with ascites, chronic hepatitis with ascites) (1) portal cirrhosis with ascites and small liver, (2) portal cirrhosis with ascites and large liver, (3) portal cirrhosis with ascites and jaundice and (4) large liver without ascites, presumably portal cirrhosis in the preascitic stage.

Biliary cirrhosis or icteric cirrhosis (cirrhosis with chronic jaundice, chronic hepatitis with jaundice) (1) biliary cirrhosis with extrahepatic obstruction, (2) biliary cirrhosis without extrahepatic obstruction and (3) biliary cirrhosis with ascites.

While we may speak of these groups as separate entities, it must be understood that these divisions are made for convenience in presentation and so are necessarily somewhat artificial. Detailed discussion, particularly of the etiology and pathology of the condition, will be reserved for later communications. The complete laboratory data of the clinical investigations are given in the accompanying tables. Abstracts of the histories of illustrative cases are also included. In these only significant laboratory data are given. The phenoltetrachlorophthalein test is reported in terms of one hour reading.

PORTAL CIRRHOSIS WITH ASCITES AND SMALL LIVER ("LAENNEC'S CIRRHOSIS")

In his "*Traite de l'auscultation mediate*," Laennec³ gave an anatomic description of cirrhosis which is classic.

The liver, reduced to a third of its ordinary size, was buried, if I may use the term, in the region which it occupies, and its external surface, slightly pursed and wrinkled, was of a yellowish-grey tint. On incision, it appeared entirely composed of a multitude of small round or ovoid grains, varying in size from that of a millet to that of a hemp-seed. There was scarcely any interval between these grains, in which they could still be distinguished from remains of the proper tissue of the liver, they were easily separable from each other, of a fawn or red-yellow color, inclining in some places to green, and of a humid, opaque tissue, flaccid rather than soft to the touch, so that on pressing the grains between the fingers a small part only crumbled away, the rest feeling in the hand like a piece of soft leather.

Rigid definition would require that the use of the term Laennec's cirrhosis be restricted to those cases of portal cirrhosis in which the liver

³ Laennec, R. T. H. *Traite de l'auscultation mediate et des maladies des poumons et du coeur*, ed 2, Paris, J. S. Claude, 1826, vol 2, p 196, *A Treatise on Mediate Auscultation and on Diseases of the Lungs and Heart*, London, H. Bailliere, 1846, p 436 (edited by T. Herbert).

was reduced in volume and would exclude those cases in which that organ was increased in size. Such a distinction is of questionable clinical or pathologic value. We mention it here because of its historical association.

The disease usually develops slowly and insidiously. There may be moderate initial nausea or bloating and dull pain or discomfort in the right hypochondrium. Occasionally slight jaundice, the "signal jaundice" of Rolleston,⁴ may be present at the time of onset. Usually these symptoms are so trifling that they are passed over unnoticed, and attention is not called to the condition until signs of altered circulation appear. The abdomen then becomes distended and fluctuant. The quantity of fluid may be so great that satisfactory palpation of the abdomen is precluded. When the fluid is removed, the liver may be found to be reduced or increased in size, while the spleen may be enlarged. Evidence of collateral circulation is seen in the enlargement of the mammary, epigastric, hypogastric and hemorrhoidal veins. Rarely is the superficial circulation so marked as to present the picture of a true caput medusae. Hematemesis or melena may occur, suggesting the presence of leaking or ruptured esophageal varices. As the condition progresses, the patient loses flesh and strength. The skin is muddy or icteric in color, and the face is thin and shrunken, contrasting markedly with the full distended abdomen. The laboratory observations in a series of typical cases of this type are given in table 1. The clinical history is illustrated in case 1.

CASE 1 (case 4, table 1)—A man, aged 63, had undergone herniotomy elsewhere in August, 1924, when free fluid was found in the abdominal cavity. Enlargement of the abdomen became noticeable soon afterward and increased progressively. Associated with the abdominal distention there was moderate edema of the feet and ankles, slight bloating and abdominal distress and loss in weight.

When the patient was first seen on Nov. 10, 1924, the emaciation of the face and arms contrasted markedly with the distention and enlargement of the abdomen. He was anemic, and the complexion was sallow though not distinctly jaundiced. Because of the marked ascites, none of the abdominal viscera could be felt. The superficial abdominal veins were dilated, and there was edema of the legs and lumbosacral region. The blood urea was 40 mg and the serum bilirubin 1.4 mg for each 100 cc. A "delayed direct" van den Bergh reaction was obtained. There was retention of phenoltetrachlorophthalein with a reading of 17 per cent.

Twelve liters of slightly turbid, straw-colored fluid was removed by paracentesis. The spleen could then be felt extending 8 cm. below the costal margin. The liver was not palpable. The fluid rapidly reaccumulated. Commencing November 20, treatment with merbaphen and ammonium chloride was instituted, a total of 12 cc. of merbaphen being given. Satisfactory diuresis followed, and on December 18 the patient weighed 150 pounds (68 Kg.), which indicated a loss of 45 pounds (20.4 Kg.). The abdominal distention had disappeared completely, and no fluid could be demonstrated. The spleen was enlarged, while the margin of the liver was palpable just at the costal margin. The evidences of collateral

4 Rolleston, H. D. *Diseases of the Liver, Gallbladder and Bile Ducts*, ed. 2, New York, The Macmillan Company, 1914, p. 811.

TABLE 1—Portal Cirrhosis with Ascites (Small Liver)

Case	Date	Age, Years	Sex	Edge of Liver Palpable, Cm*	Ascites, Grade 0 to 4	Duration of Ascites, Months	Spleen Enlarged, Grade 0 to 4	Specific Gravity	Urine		Blood Count			Phenolsulphonphthalein, Per Cent	Blood Nitrogen Partition Mg for Each 100 Cc				Bile Pigments (Serum)	Fructose Tolerance Blood Sugar Mg for Each 100 Cc			Phenolphthalein Dye in Serum, per Cent			Comment						
									Albumin	Bile Pigments	Hemoglobin Per Cent	Erythrocytes, Millions	Leucocytes		Urea	Uric Acid	Creatinine	Amino Acid Nitrogen		Serum Bilirubin, Mg for Each 100 Cc	Van den Bergh Direct Reaction	Fasting	One Hour	Two Hours	Change		Fifteen Minutes	One Hour	Two Hours	Dye in Urine, Mg		
1	7/2/24	62	M	0	3	2	2	0	1.019	1	63	3.18	7,000	70	30	13	32	20	5.6	2.9	+	86	115	106	18	18	20	17	17	11	0.9	Cirrhosis observed at operation
2	3/26/23	42	M	0	3	6	1	0	1.026	0	67	3.72	4,600	70	20	24	0.8	7.0	2.9	+	86	115	106	18	18	18	18	18	18	18	Necropsy, weight of liver, 992 Gm	
3	1/8/25	27	F	0	3	4	0	0	1.010	1	65	3.62	4,600	50	35	28	11	5.5	0.6	++	89	135	102	44	11	15	10	0.3	0.3	0.3	Cirrhosis observed at operation	
4	11/21/24	63	M	0	3	5	2	0	1.025	1	55	3.46	3,000	45	38	11	2.5	1.4	1.1	++	89	135	102	44	11	15	10	0.3	0.3	0.3	Cirrhosis observed at operation	
5	12/1/24		+	+	1	2	0	1.014	0	60	4.00	6,600		23	31	2.9	1.5	5.6	1.6	++	89	135	102	44	11	15	10	0.3	0.3	0.3	Cirrhosis observed at operation	
6	12/18/24		+	+	0	2	0	1.018	1	60	3.38	6,600		65	12	13		1.8	1.8	++	89	135	102	44	11	15	10	0.3	0.3	0.3	Cirrhosis observed at operation	
7	4/2/25		+	+	1	2	0	1.027	0	58	2.74	3,300		34				0.9	0.9	++	89	135	102	44	11	15	10	0.3	0.3	0.3	Cirrhosis observed at operation	
8	7/9/25		+	+	2	0	1.018	0	1.018	0	40	2.14	3,300	45	71	10	1.7		0.7	0.7	++	89	135	102	44	11	15	10	0.3	0.3	0.3	Cirrhosis observed at operation
9	9/2/25	36	M	+	3	1	0	1.020	0	37	3.02	3,700		50	15	18		2.9	2.9	++	89	135	102	44	11	15	10	0.3	0.3	0.3	Cirrhosis observed at operation	
10	9/2/25	36	M	0	3	3	1	0	1.020	0	50	3.17	5,000	45	15	18			2.9	2.9	+	89	135	102	44	11	15	10	0.3	0.3	0.3	Cirrhosis observed at operation
11	1/8/25	48	M	+	3	11	1	0	1.019	0	65	3.80	4,800	50	28	15	2.3	1.2	6.1	1.6	+	89	135	102	44	11	15	10	0.3	0.3	0.3	Cirrhosis observed at operation
12	4/3/23	60	M	0	2	1	1	0	1.014	4	76	4.58	9,600	50	30	30		6.9	6.9	+	89	135	102	44	11	15	10	0.3	0.3	0.3	Cirrhosis observed at operation	
13	9/19/24	37	F	0	3	18	1	0	1.030	0	68	3.85	5,300	40	25	18	1.9	1.5	5.1	1.1	0	123	95	95	28	8	7	18	18	18	Cirrhosis observed at operation	
14	2/15/24	68	M	0	3	4	0	0	1.025	1	72	4.26	5,300	35	11	21	1.1	1.1	1.0	0	145	156	104	11	9	8	5	0.5	0.5	0.5	Cirrhosis observed at operation	
15	6/25/24	60	M	0	3	6	1	0	1.023	1	70	4.37	7,000	20		12	2.0	1.5	0.1	0				10	6	5	0.5	0.5	0.5	Cirrhosis observed at operation		
16	3/10/24	42	F	+	3	4	1	0	1.023	1	70	4.80	11,000	40	29	24			1.2	0	110				6	3	1	10	10	10	Cirrhosis observed at operation	
Portal Cirrhosis with Ascleites and Jaundice																																
17	7/30/24	58	F	0	1	1	0	1	1.011	2	73	4.38	7,200	50	15	59	1.3	7.0	32.8	+	108				35						Necropsy, weight of liver, 817 Gm	
18	3/17/25	64	F	0	4	1	0	1	1.010	1	64	3.07	8,400		16	33	1.2		4.6	+	112				22	28	25	12	12	12	Necropsy, weight of liver, 830 Gm	
19	5/26/24	54	F	+	2	5	0	1	1.017	1	45	2.88	7,800		25	21	1.7	1.2	5.4	13.6	+	93	147	135	54	20	20	20	20	20	20	

* + indicates barely palpable

† + indicates a "prompt" direct reaction, and 0, an indirect reaction

circulation over the abdomen vanished. At this time the serum bilirubin was 1.8 mg. The phenoltetrachlorophthalein reading was 20 per cent.

The patient was dismissed in good condition. He continued to feel well and was strong and active. He returned on March 19, 1925, because of a slight gain in weight and abdominal enlargement. He weighed 10 pounds (4.5 Kg.) more than at the time of his dismissal, and a small amount of fluid could be demonstrated in the abdomen. His general appearance was much improved, otherwise examination showed his condition to be the same as when he was dismissed three months before. The serum bilirubin was 0.9 mg., with a delayed direct van den Bergh reaction. The dye retention was 10 per cent. Three injections of merbaphen produced marked diuresis and a total loss of 15 pounds (6.8 Kg.) in weight. The patient continued to improve following his dismissal until June 8, 1925, when he had a severe gastric or esophageal hemorrhage. He was weakened and confined to his bed for ten days at that time, but had been well thereafter. Because of weakness and a reduction of hemoglobin to 40 per cent, he was given a transfusion of 500 cc. of citrated blood on July 10.

On Sept. 2, 1925, the erythrocytes had increased to 3,020,000. The serum bilirubin was 0.7 mg. with an indirect van den Bergh reaction. The phenoltetrachlorophthalein reading was 4 per cent. Since then he has been able to carry on his usual activity, although progressive loss of strength has been associated with recurring gastro-intestinal hemorrhages, and the ascites has been more difficult to control.

This case has been of interest because of the prolonged period of observation and the unusually complete control of the ascites under treatment with merbaphen. It will be noted that there was no immediate change in the degree of dye retention during the period of removal of the ascitic fluid. This would seem to eliminate changes due to passive congestion of the liver such as were observed in case 17 (table 2). Subsequently the amount of dye retention has progressively decreased. This improvement in hepatic function indicated by the phenoltetrachlorophthalein test is important, for it suggests that there may have been regenerative changes in the liver during the period of observation. This case is also of interest in that alcohol could be excluded as a possible etiologic agent.

The laboratory observations in the other cases in this group were similar. The bromsulphthalein test was normal in one case, but in all the others this test showed a varying degree of retention of the dye. In two cases a slight increase in the serum bilirubin indicated the presence of latent icterus. A "prompt" or "delayed" direct van den Bergh reaction was obtained in the majority of instances even though the serum bilirubin was not increased.

PORTAL CIRRHOSIS WITH ASCITES AND LARGE LIVER

An increase in the size of the liver is readily distinguishable in many cases of portal cirrhosis. When abdominal distention is marked, it may be impossible to feel the liver, and it is only after relief from the ascites that the condition can be recognized. At present there is no other clear-cut distinction between this group and the preceding one, in which

the liver is reduced in size. The extent of parenchymal degeneration, the proliferative changes in the connective tissue, the contraction of scar tissue, the amount of hepatic regeneration and the presence or absence of fatty changes are the important factors which influence the size of the liver. For obvious reasons these factors will not be discussed in this communication.

The cases included in this group differ from those listed as of the Laennec type in that the edge of the liver was palpable at or several centimeters below the costal margin. The clinical histories are similar in the two series of cases. Enlargement of the liver from other causes, especially from cardiac failure with chronic passive congestion, must be excluded. Apart from the influence of such associated conditions, the size of the liver is of questionable value in the clinical classification of portal cirrhosis. The results of the different functional tests are shown in table 2. The clinical history is illustrated in cases 2 and 3.

CASE 2 (case 23, table 2) —A man, aged 38, came to the clinic on Oct. 18, 1920, because of a moderate loss of weight during the preceding year. He was constipated and complained of occasional "biliousness" and indefinite distress in the upper part of the abdomen. The edge of the liver was palpable at the costal margin. The patient was nervous and of introspective temperament. The diagnosis was indeterminate at that time. Six months later, pneumonia was followed by empyema which necessitated drainage. The patient was well for awhile, but in 1922 began to feel listless. His physician removed 6 liters of fluid from the abdomen at that time, and paracentesis was again carried out before readmission to the clinic on Oct. 1, 1923.

The abdomen was distended and tense, and the superficial abdominal vessels were dilated. After paracentesis and the removal of 3 liters of amber colored fluid, the edge of the liver could be felt 10 cm. below the costal margin, while the spleen was just palpable. The patient was not anemic. The specific gravity of the urine was 1.014, and only a trace of albumin was present. The blood urea was 43 and the fructose tolerance was normal. There was slight retention of dye, with a reading of 5 per cent.

Laparotomy was performed on Oct. 31, 1923, when 10 liters of ascitic fluid was removed. The liver was large and said by the surgeon to be cirrhotic. The spleen was about twice the normal size. It was removed and a Talma-Morison operation performed. Convalescence was uneventful. Fluid reaccumulated slowly at first, and paracentesis was necessary a month later. Thereafter recovery was uneventful. Three years later this patient reported himself in good health, free from ascites and again able to carry on his business.

CASE 3 (case 17, table 2) —A man, aged 63, first came to the clinic on Jan. 20, 1925, because of abdominal distention, which had come on two years before. Previously he had enjoyed good health, although he was a heavy user of alcohol. The onset of the illness was gradual, the distention first being noted in November, 1922. Subsequently paracentesis was carried out on eight occasions, from 8 to 10 liters of light-colored fluid being removed each time. The relief following such a tapping lasted for from five to six weeks. In August, 1924, a physician elsewhere administered calcium chloride as a diuretic. Seventy pounds (31.8 Kg.) were lost in four weeks, but the ascites returned when the calcium chloride was discontinued.

The patient's weight on admission was 250 pounds (113.4 Kg.), 60 pounds (27.2 Kg.) more than his best normal weight. There was marked ascites, and it was impossible to palpate any of the abdominal viscera. There was definite peripheral

arteriosclerosis, and the heart was somewhat enlarged. Considerable edema of the scrotum and legs was present.

There was moderate secondary anemia. An electrocardiogram showed auricular fibrillation, right ventricular preponderance and inversion of the T-wave in leads I and II. The specific gravity of the urine was 1.030, and a trace of albumin and casts were present. The blood urea was 54 mg and the serum bilirubin 2.1 mg. A direct van den Bergh reaction was obtained. The retention of phenoltetrachlorophthalein was 25 per cent.

The patient was put on a low protein, salt-free diet, and the fluid intake was restricted. In addition, 10 Gm of ammonium chloride was given daily, and merbaphen intravenously every fourth day. Improvement was rapid and striking. On February 13, after a total of 4 cc of merbaphen had been taken, the patient's weight was 175 pounds (79.4 Kg), a loss of 75 (34 Kg) pounds. At this time the heart was regular and the edema of the extremities had disappeared, although digitalis had not been given or other specific cardiac medication instituted. Fluid could not be demonstrated in the abdomen. The edge of the liver could be felt 8 cm below the costal margin, and the spleen was palpable 5 cm below the left costal margin. The blood urea was 21 mg and the serum bilirubin 1.6 mg, with a direct van den Bergh reaction. There was marked improvement in the phenoltetrachlorophthalein test with a reading of 10 per cent.

The patient continued to improve in strength and health while under observation. On March 3, the weight was 160 pounds (72.6 Kg), indicating a total loss of 90 pounds (40.8 Kg) during treatment. The serum bilirubin was 2.1 mg and the dye retention 10 per cent. The patient was dismissed in good condition. He returned on June 23, 1926, for reexamination, having been in good health and free from ascites during the intervening period. The liver was reduced somewhat in size, extending only 2 cm below the costal margin, and the spleen was no longer palpable. The blood urea was 31 mg. The serum bilirubin was 1.8 mg and the van den Bergh reaction indirect. The phenoltetrachlorophthalein test gave a reading of 8 per cent.

When this patient was first seen, decompensation with passive congestion was superimposed on the cirrhosis. With the recovery of compensation and the disappearance of the hepatic congestion, the degree of dye retention decreased rapidly from 25 to 8 per cent. Thereafter the phenoltetrachlorophthalein test did not change. We believe that this sequence demonstrates both the temporary effect of passive congestion and the more permanent effect of cirrhosis on the excretion of dye. These observations are analogous to those of the phenolsulphonphthalein test in passive congestion superimposed on chronic nephritis.

These two cases serve to illustrate the functional changes observed in the nine cases included in this group. Retention of dye was uniformly present though to a varying degree. The serum bilirubin was occasionally increased to a degree indicating the presence of latent icterus, but for the most part it varied around the upper limits of the normal. A direct van den Bergh reaction was obtained in the majority of cases. The changes in the other laboratory tests were not striking, and will be discussed later.

PORTAL CIRRHOSIS WITH ASCITES AND JAUNDICE

Jaundice is an occasional but not a prominent symptom in portal cirrhosis. When "signal jaundice" is observed at the onset of the condition, it is usually of slight degree and transitory. During the progress of the malady the skin may acquire the muddy yellow or subicteric hue

that is so characteristic a feature of the hepatic facies. Manifest and outspoken jaundice, on the other hand, is uncommon and is usually considered a late or terminal event. Such cases, both clinically and from the point of view of the gross pathology, may present a picture distinguishable with difficulty from that seen in the end stages of biliary cirrhosis with terminal ascites. Differentiation must be made largely on the basis of the chronologic sequence of events in the history.

CASE 4 (case 13, table 1) —A woman, aged 64, was admitted to the clinic on March 17, 1925, because of ascites and jaundice of two months' duration. In January, 1925, she first noted weakness and loss of strength, which increased progressively. In February, she began to feel that the abdomen was getting larger, there was also some swelling of the ankles. Shortly afterward jaundice appeared, but she did not have pain, fever or pruritus. The stools became lighter and the urine dark. The jaundice never became extreme and diminished slightly in intensity. The ascites increased, however, and strength failed rapidly.

The abdomen was greatly distended with marked ascites. The abdominal viscera could not be felt. There was edema of the lower abdominal wall and of the lower extremities. Moderate jaundice was evident. The urine contained bile and a trace of albumin. There was moderate secondary anemia. The serum bilirubin was 4.6 mg, and a direct van den Bergh reaction was obtained. There was retention of phenoltetrachlorophthalein with a reading of 28 per cent.

A Talma-Morison type of omentopexy was performed in an attempt to relieve the ascites. The surgeon reported the presence of advanced cirrhosis of the liver. The patient did not rally following the operation, but went into coma, the blood urea rapidly rose to 130 mg, and death occurred on the fourth day after operation. At necropsy the liver was found to weigh but 850 Gm.

The laboratory data in three cases are given in table 1. As would be expected from the presence of jaundice, the serum bilirubin was increased, and a direct van den Bergh reaction such as is encountered in obstructive jaundice was obtained. The retention of dye likewise was marked.

PORTAL CIRRHOSIS WITHOUT ASCITES

Obviously, the question of the early stage of portal cirrhosis has been omitted from consideration. In the absence of evidence of collateral circulation and ascites, it is difficult to be certain of the nature of the changes in an individual case. However, under certain conditions, particularly among heavy drinkers, the diagnosis at times may be made clinically with a reasonable degree of certainty. If the liver is enlarged, the possibility of chronic hepatitis or early cirrhosis must be considered in the diagnosis.

The common textbook picture of cirrhosis is that of the so-called "gin drinker's liver." While suggested by clinical observations, the presence of a direct etiologic relationship between cirrhosis and alcohol is by no means firmly established, and in several of the cases reported in this series we could not secure a history of alcoholism or of the use of alcohol in any form. On the other hand, we present here a case illustrative of a small group in which the associated enlargement of the

liver can best be explained on the basis of the history of prolonged and intensive abuse of the use of alcohol. It is impossible to distinguish between the relative rôle of hypertrophy and that of fatty infiltration in such enlargement without making a microscopic examination. Extended clinical observation, likewise, is necessary to prove that ascites is a later complication in such cases. Nevertheless, the implication remains that these cases represent an early stage of the group discussed as the hypertrophic form of portal cirrhosis without ascites. Our studies include seven cases in this group. The laboratory observations are shown in table 2, and the history of one case of this type is given. The cases are included as representing the early changes of portal cirrhosis. Thus we must admit is presumptive, and the true nature of the hepatic disease not known.

CASE 5 (case 26, table 2)—A man, aged 25, was admitted to the clinic on Jan 15, 1924, because of discomfort of three months' duration in the right side of the upper part of the abdomen. He was the son of a saloon-keeper and was a "bootlegger" by occupation. He had been a steady drinker from the age of 10 and for several years had averaged one pint of whisky a day. Three months before admission, he began to have pain and discomfort along the right costal margin. This pain was continuous but never severe, except on two or three occasions when it became disabling. He vomited then and had diarrhea for a few days. He did not have jaundice at any time.

On examination the liver was found to extend 12 cm below the costal margin. It was firm and not tender. The spleen was not palpable. Urinalysis showed only a trace of albumin. The blood count was normal. A fractional test meal showed absence of free hydrochloric acid. Fluoroscopic examination of the stomach was negative. The serum bilirubin was 0.7 mg. There was slight retention of phenoltetrachlorophthalein with a reading of 5 per cent.

While the clinical picture in this case is somewhat indefinite, the history of pronounced and persistent alcoholism and the enlargement of the liver makes the presence of cirrhosis probable.

NOTE.—The patient returned to the clinic in February, 1927. At that time there was marked ascites, and he presented a clinical appearance of a typical portal cirrhosis with ascites and an enlarged liver.

BILIARY CIRRHOSIS WITH EXTRAHEPATIC OBSTRUCTION

While ascites and the development of collateral circulatory channels are the chief signs of interference with the portal circulation and so of portal cirrhosis, jaundice is equally indicative of the disturbance in biliary secretion that accompanies biliary cirrhosis.

The best known type of chronic hepatitis with jaundice is the biliary cirrhosis produced by occlusion of the common bile duct. This has been produced experimentally by Wickham Legg,⁵ Harley and Barratt,⁶

5 Legg, J. Wickham. On the Changes in the Liver Which Follow Ligature of the Bile Ducts, *St Barth Hosp Rep* 9 161, 1873.

6 Harley, V., and Barratt, W. The Experimental Production of Hepatic Cirrhosis, *J Path & Bact* 7 203, 1901.

TABLE 2.—Portal Cirrhosis with Ascites (Large Liver)

Case	Date	Age Years	Sex	Urine				Blood Count			Blood Nitrogen Portion Mg for 100 Cc				Bile Pigments (Serum)		Fructose Tolerance Blood Sugar Mg for Each 100 Cc			Phenoltrichlorophthalein			Comment
				Specific Gravity	Albumin	Hemoglobin, Per Cent	Erythrocytes, Millions	Leucocytes	Phenolsulphonphthalein, Per Cent	Urea	Uric Acid	Creatinine	Amino Acid Nitrogen	Serum Bilirubin, Mg for Each 100 Cc	V in den Berg's Direct Reaction*	Normal	One Hour	Two Hours	Change	Fifteen Minutes	Dye in Serum, per Cent	Dye in Urine, Mg	
15	3/24/24	33	F	1.024	1	88	556	6,000	88	29	11	19	14	63	18	0	90	123	119	32	25	20	Cirrhosis observed at operation
16	4/10/24	55	F	1.018	1	87	555	7,100	50	26	10	20	12	63	43	0	90	123	119	32	19	15	Merbaphen 4 cc., loss of weight, 70 lbs
17	4/28/25	55	F	1.016	1	88	375	8,000	50	40	32	24	10	64	47	++	90	123	119	32	28	17	Merbaphen 6 cc., loss of weight, 81 lbs
17	4/9/25	55	F	1.032	1	75	436	6,000	53	19	27	17	17	36	36	++	90	123	119	32	22	18	Fifteen months later
17	1/21/25	62	M	1.030	0	70	381	5,200	40	54	38	22	59	21	+	+	90	123	119	32	25	22	Merbaphen 2 cc
17	2/13/25	63	M	1.022	0	70	363	9,200	40	21	38	22	59	16	+	+	90	123	119	32	25	22	Cirrhosis observed at operation
17	2/13/25	63	M	1.022	0	70	363	9,200	40	21	38	22	59	16	+	+	90	123	119	32	25	22	Cirrhosis observed at operation
18	3/3/25	8	0	1.022	0	80	1,010	1,010	40	11	31	25	14	21	+	+	90	123	119	32	10	10	Cirrhosis observed at operation
18	6/23/26	47	M	1.022	0	87	196	7,900	50	11	31	16	16	68	18	0	90	123	119	32	19	15	Merbaphen 2 cc
19	11/10/24	47	M	1.031	0	72	360	1,000	55	28	17	20	15	52	19	0	90	123	119	32	25	20	Cirrhosis observed at operation
19	11/21/24	55	M	1.024	1	75	392	1,000	65	31	20	22	11	58	+	+	90	123	119	32	30	22	Cirrhosis observed at operation
20	4/28/25	55	M	1.020	0	58	249	3,500	65	31	20	22	11	58	+	+	90	123	119	32	30	22	Cirrhosis observed at operation
20	11/1/24	63	F	1.010	0	70	141	1,500	65	31	20	22	11	58	+	+	90	123	119	32	14	17	Cirrhosis observed at operation
21	5/12/24	48	M	1.030	1	70	116	5,700	65	29	31	16	11	23	0	+	90	123	119	32	13	13	Cirrhosis observed at operation
22	4/9/24	50	M	1.023	0	70	125	6,100	65	19	13	16	17	06	+	+	90	123	119	32	10	10	Cirrhosis observed at operation
23	10/1/23	41	M	1.014	1	85	175	5,000	65	13	16	17	17	06	+	+	90	123	119	32	10	10	Cirrhosis observed at operation
24	11/5/24	51	M	1.024	0	78	513	8,300	10	27	23	16	16	18	+	+	90	123	119	32	11	11	Cirrhosis observed at operation
25	10/16/23	53	M	1.008	1	52	110	6,700	10	27	23	16	16	18	+	+	90	123	119	32	11	11	Cirrhosis observed at operation
26	1/15/24	25	M	1.021	1	78	435	1,000	10	27	23	16	16	18	+	+	90	123	119	32	11	11	Cirrhosis observed at operation
27	1/16/25	54	M	1.021	0	72	113	7,300	10	27	23	16	16	18	+	+	90	123	119	32	11	11	Cirrhosis observed at operation
28	2/3/25	42	M	1.027	0	85	166	6,000	10	27	23	16	16	18	+	+	90	123	119	32	11	11	Cirrhosis observed at operation
29	3/16/25	40	M	1.010	2	51	368	12,500	10	12	11	13	13	01	0	+	90	123	119	32	7	3	Cirrhosis observed at operation
30	4/20/25	53	M	1.016	0	60	124	11,000	60	19	13	13	13	01	0	+	90	123	119	32	3	1	Cirrhosis observed at operation

* + indicates a 'prompt' direct reaction, ±, "delayed" direct reaction, and 0, in indirect reaction

Charcot and Gombalt,⁷ Ogata⁸ and others Mangelsdorff,⁹ Ford,¹⁰ Weber¹¹ and others have summarized the clinical observations on patients with complete obstruction of the extrahepatic bile ducts and, further, have emphasized the similarity to the changes observed in animals Ford pointed out that this form of cirrhosis cannot be explained wholly by the damming back of bile, but that an added etiologic factor is present in the inflammation of the walls of the biliary channels Originally reported as the result of complete biliary obstruction, the condition now is more frequently found in patients with recurring biliary colic and intermittent obstruction W J Mayo¹² has especially emphasized the importance of considering biliary cirrhosis the end-result of infectious and obstructive processes secondary to disease of the gall-bladder or common bile duct

The clinical features of such cases are usually distinct Most characteristic is the long-continued history of recurring attacks of temporary of incomplete biliary obstruction, usually from gallstones Temporary jaundice commonly accompanies these attacks Clinical evidence of infection with chills or so-called hepatic or Charcot fever is common The length of the history and the failure of the jaundice to disappear completely between attacks speak for the presence of permanent hepatic damage

CASE 6 (case 42, table 3)—*Chronic Cholangitis with Choledocholithiasis* A man aged 65, came to the Clinic on March 8, 1924, having suffered from chills and fever for six years Ten years before, there were irregular attacks of bilateral pain in the upper part of the abdomen associated with nausea and vomiting These occurred at intervals for two years, then ceased temporarily Six years before admission he again began to have intermittent painless attacks beginning with a chill and followed by fever, profuse perspiration and prostration Recovery usually took place within twenty-four hours Jaundice occurred regularly during the attacks, icterus sometimes preceding the chill Following this the urine would be dark for a day or so The stools occasionally were light but never clay-colored The jaundice was never extreme, but, on the other hand, never disappeared completely between attacks The complexion was dark and the skin brownish yellow The liver was slightly enlarged, and the edge was

7 Charcot and Gombalt Note sur les alterations du foie consecutives a la ligature du canal choledoque, Arch de physiol norm et path **18** 272, 1876

8 Ogata, Tomosaburo Beitrage zur experimentell erzeugten Lebercirrhose und zur Pathogenese des Ikterus mit spezieller Berücksichtigung der Gallenkapillaren bei der Unterbindung des Ductus Choledochus und der Ikterogenvergiftung, Beitr z Path Anat u z allg Pathol **55** 236, 1913

9 Mangelsdorff, J Ueber biliare Lebercirrhose, Deutsches Arch f klin Med **31** 522-603, 1882

10 Ford, W W Obstructive Biliary Cirrhosis, Am J M Sc **121** 60, 1901

11 Weber, F Parkes On Biliary Cirrhosis of the Liver with and Without Cholelithiasis, Tr Path Soc London **54** 103, 1903

12 Mayo, W J The Surgical Treatment of the Cirrhoses of the Liver and Their Complications, Ann Surg **68** 183, 1918, The Liver and Its Cirrhoses, J A M A **70** 1361 (May 11) 1918, Surgical Treatment of Hepatic Cirrhoses, Ann Surg **80** 419, 1924, The Liver and Its Cirrhoses, J Iowa M Soc **16** 299, 1926

rounded but not tender. The urine contained urobilin but no bile. There was moderate secondary anemia. The serum bilirubin was 1.8 mg. A direct van den Bergh reaction was obtained. The fructose tolerance was reduced, and there was retention of dye with a reading of 17 per cent.

At operation a large stone was found in the common bile duct together with a fistulous connection between the common bile duct and the duodenum. The stones were removed and the fistula closed. The patient did well for a time, but bronchopneumonia developed, and he died on the tenth day. At necropsy marked biliary cirrhosis was found. The liver weighed 1,442 Gm.

The laboratory observations in this case are characteristic of those in the thirteen cases comprising this group. Retention of bromsulphonphthalein was constant and marked. The serum bilirubin in general was slightly increased, though not to a proportionate extent. A reading of 10 mg. was seen in one case, and values within the normal limits were obtained in three. A direct van den Bergh reaction was obtained in all.

BILIARY CIRRHOSIS WITHOUT EXTRAHEPATIC OBSTRUCTION

Besides the obstructive type of biliary cirrhosis, there is another form in which there is no demonstrable obstruction of the extrahepatic bile ducts. There has been much uncertainty with regard to the diagnosis and classification of such cases. However, there unquestionably does exist a type of cirrhosis in which the liver is enlarged, firm in consistency, and in which no demonstrable obstruction of the hepatic bile ducts can be found at exploration or necropsy. The spleen is also enlarged, sometimes to a greater extent than is common in either the obstructive type of biliary cirrhosis or in portal cirrhosis. Chronic jaundice of variable degree persists throughout the course of the disease. In these cases, W. J. Mayo considers splenectomy of value if not too long postponed. He has also emphasized the frequency with which hemolytic jaundice and splenic anemia have been confused with this condition in the past, although the marked pruritus of the biliary cirrhosis should be of diagnostic significance. The melanoderma or pigmentation of the skin which is present, in addition to the staining with the bile pigments, is also characteristic.

This form of biliary cirrhosis is undoubtedly related to that described by Hanot¹³. The descriptions of the latter are not entirely clear, and there is not at present any sharply defined clinical and pathologic entity to which this name may be applied. A probable relationship to the cases of subacute hepatitis or intrahepatic jaundice, such as those reported from this service by Weil, must be admitted. It has seemed best, therefore, to avoid sharply defined differentiations or eponymic terms in discussing this group and to refer to the cases as examples of primary or nonobstructive biliary cirrhosis as previously pointed out. Table 3 presents data relating to four such cases, one of which is presented in detail as follows:

¹³ Hanot, V. La cirrhose hypertrophique avec ictère chronique, Paris, Rueff et Cie, 1892, p. 182.

CASE 7 (case 46, table 3)—A woman, aged 42, first came to the clinic on Aug 22, 1924, because of abdominal distress of two years' duration. She had never been strong and had been troubled with nausea, anorexia, smothering sensations and other symptoms for many years. In 1920 eight teeth were removed, which necessitated six injections of serum for hemostasis. Three weeks later, the right antrum became infected, soon afterward generalized pruritus appeared and persisted for several months before icterus was noted. The jaundice was slight and variable in degree, but was associated with rather marked bronzing of the skin. In 1922 pressure in the right upper quadrant of the abdomen caused soreness, later there were occasional chills, which were accompanied by pain along the right costal margin and an intensification of the jaundice for several days. In January, 1923, one ovary was excised elsewhere, the gallbladder was reported normal and was not disturbed. The symptoms recurred rapidly, with bloating, epigastric soreness, slight jaundice and increased pigmentation of the skin. In March, 1924, a second operation was performed elsewhere, and the spleen was found to be enlarged. A section of the liver removed for microscopic examination showed biliary cirrhosis with diffuse infiltration of round cells, which was most intense in the periphery of the lobule.

The patient was an asthenic, undernourished woman with slight yellowish discoloration of the sclerotics and marked generalized brownish pigmentation of the skin. The color of the skin suggested Addisonian pigmentation, although it did not have the characteristic distribution. The spleen was palpable 10 cm below the costal margin. The liver extended 5 cm below the costal margin and was smooth and firm, regular in outline, but slightly tender. Renal function was excellent. The serum bilirubin was 2.1 mg, and a direct van den Bergh reaction was obtained. There was retention of phenoltetrachlorophthalein with a reading of 20 per cent. Because of the evidence of hepatic damage found at the previous operation further intervention was postponed, but the patient was kept under observation.

She returned on March 20, 1925 because of persistence of the pruritus, slight jaundice and abdominal pains. She was stronger than when first seen, but there had not been any change in her color. The liver was unchanged, but the spleen appeared to be slightly larger than before. The serum bilirubin was 1.7 mg, and there was dye retention of 13 per cent.

At operation March 26, 1925, an enlarged, somewhat vascular liver was found. There were many adhesions from the former operation with thickening in the region of the common duct but no stones could be felt. The spleen was large and soft but was removed without difficulty. Microscopic examination of the spleen showed fibrosis with subacute splenitis.

The postoperative recovery was uneventful. The subicteric color of the skin disappeared in part, but the pruritus persisted. Two weeks after the operation, the serum bilirubin was 0.8 mg. Retention of dye, however, persisted with a reading of 19 per cent.

Seven series of tests were made in four cases. In all there was retention of dye. As in the cases of obstructive biliary cirrhosis the serum bilirubin was slightly, though not markedly, increased, and the van den Bergh reaction was direct.

BILIARY CIRRHOSIS WITH ASCITES

Although jaundice and ascites are present in this group, as in the group already discussed under portal cirrhosis, the relation of the two symptoms is somewhat different. In the present group jaundice has constituted a marked clinical feature of the disease, the ascites as a rule being of late occurrence.

TABLE 3—*Biliary Cirrhosis with Extrahepatic Obstruction*

Case	Date	Age, Years	Sex	Edge of Liver Palpable, Cmn *	Jaundice, Grade 0 to 4	Intermittent Jaundice, Duration, Years	Spleen Enlarged, Grade 0 to 4	Ascites	Urine			Blood Count			Phenolsulphonphthalein, Per Cent	Blood Nitrogen Partition, Mg for Each 100 Cc					Bile Pigments (Serum)	Fructose Tolerance Blood Sugar Mg for Each 100 Cc			Phenolterra chlorophthalein			Comment				
									Specific Gravity	Albumin	Bile Pigments	Hemoglobin, Per Cent	Erythrocytes, Millions	Leukocytes		Nonprotein Nitrogen	Urea	Uric Acid	Creatinine	Amino-Acid Nitrogen		Serum Bilirubin, Mg for Each 100 Cc	V in den Bergh	Direct Reaction	Normal	One Hour	Two Hours		Change	Fifteen Minutes	One Hour	Two Hours
31	7/ 5/24	50	F	+	1	5	0	0	1.025	1	—	60	366	5,600		34	39	38	19	58	38	+					36	34	34	13	Cholecholethiasis, operation	
32	8/14/24	66	M	4	2	4	0	0	1.022	1	+	71	403	8,000	70	38	41	35	15	48	57	+	101	123	103	22	25	33	25	42	Cholecholethiasis, operation	
33	8/22/24 9/17/24	61	M	4 +	2 2	40	0	0	1.003	0	—	65	386	5,100		40 21	47 17	46 32	20 18	19 15	51 55	+	+	95	123	137	42	34	24	22	30	Cholecholethiasis, operation
34	2/25/25	47	F	4	2	10	1	0	1.024	0	+	76	414	6,900	45	28	27	25	16		41	+	112				22	26	26	18	Cholecholethiasis, operation	
35	6/ 9/24	49	F	2	+	1	0	0	1.020	0	0	77	400	6,700		24	27	25	15	50	25	+	86	146	100	60	23	25	17	15	Postoperative stricture, operation	
36	2/14/25	62	M	10	+	10	1	0	1.026	0		76	154	4,800	60		12	30	11		49	+					15	25		11	Chroniccholecystitis, operation	
37	3/ 4/25	56	F	+	+	15	0	0	1.022	0		75	103	6,300			16	35	14		14	+					20	23	20	13	Cholecholethiasis, operation	
	3/20/25			+	0											27	25	13		10	+					10	15	13	22	Fifteen days after operation		
38	6/17/23	62	F	+	+	10	1	0	1.016	1		61	390	17,200	60		19	16	15	55							20	20	20	03	Cholecholethiasis, necropsy	
39	7/ 7/21	41	F	10	3	10	0	0	1.025	1	+	57	340	5,300		28	25	21	13	63	104	+	84	107	72	23	17	20	17	75	Postoperative stricture, operation	

10	7/29/24	73	M	+	1	5	1	0	1 0 2 1	1	0	70	1 20	7,100	60	29	25	2 1	1 5	5 1	1 5	+	56	1 13	89	47	22	17	Chronic cholecystitis, necropsy		
11	9/ 1/24	57	F	6	±	10	0	0	1 0 1 0	0	0	65	3 37	6,200	60	27	9	2 1	1 3	5 5	2 6	+				17	17	15	18	Cholelithiasis, operation	
12	4/15/24	65	M	+	±	6	0	0	1 0 2 0	1	0	63	3 52	8,500		27	21	2 9	1 1	5 9	1 8	+	109	142	115	3	10	17	11	0 6	Cholelithiasis, necropsy
13	7/12/24	31	F	6	±	5	2	0	1 0 2 2	0		50	3 21	12,700	50	26	20	1 9	1 2	5 8	2 6	+	91	106	90	12	12	11	5 4	Chronic cholecystitis, operation	
Biliary Cirrhosis Without Intrahepatic Obstruction																															
44	1/ 3/24	22	M	15	2	3	3	0	1 0 1 8	2	+	55	2 79	6,600	40		10				7 6	+				17	25	25		Cirrhosis observed at operation	
45	10/21/24	60	M	2	±	0	0	0	1 0 1 1	0		72	1 01	7,600		25	29	3 0	1 6	6 5	2 4	+				11	20	15	1 2	Cirrhosis observed at operation	
16	10/27/24			2	±		0	0	1 0 0 5	0						25	15	2 2	1 7	6 1	3 9	+				17	23	12	1 8	Cirrhosis observed at operation	
	8/30/24	12	F	5	2	2	1	0	1 0 1 2	1	—	72	1 20	5,300	75		32	3 8	1 3		2 1	+				20	20				
	3/19/25			5	1	2	0	0	1 0 2 6	1	+	70	3 71	5,700	40		13	1 5	1 2		1 7	+	81			12	13	11	1 1		
	4/ 8/25			2	0		0							17,200		21					0 8	+	63			15	16	12	1 9	Two weeks after splenectomy	
17	12/13/23	46	F	10	1	12	2	0	1 0 1 6	1	0	70	1 56	7,000							2 1	+				18	12	3 4			
Biliary Cirrhosis with Ascites																															
18	6/21/25	59	F	+	3	2	1	+	1 0 2 1	0	+	47	3 69	4,600			29	1 7	1 2		12 5	+				30	27	25		Ascites three weeks, obstructive type, chronic cholecystitis, operation	
49	8/ 6/24	57	F	0	±	10	0	+	1 0 1 0	0		77	1 09	7,800		26	16	2 2	1 1	1 9	4 3	+	79	1 23	106	44	12	17	12	1 7	Cholelithiasis, ascites, obstructive type observed at operation
50	12/ 3/24	53	M	8	1	8	3	+	1 0 2 6	0		59	3 65	4,600			25	3 3	1 5		3 5	+				12	27	22	11 5	Ascites three years, nonobstructive type	

* + indicates barely palpable

† + indicates a "prompt" direct reaction, ±, "delayed" direct reaction, and 0, an indirect reaction

This combination of cirrhosis with icterus and ascites in each case represents, as a rule, the end stage with the maximum of hepatic damage. The clinical and pathologic pictures in these different conditions are usually characteristic, though mixed or intermediate forms are frequent. In this terminal period, however, distinctions disappear and differentiation must be made largely on the basis of the history.

CASE 8 (case 49, table 3) —*Biliary Cirrhosis with Extrahepatic Obstruction and Ascites*. A woman, aged 57, came to the Mayo Clinic on Aug 6, 1924, because of attacks of biliary colic which had recurred for ten or twelve years. The attacks of severe epigastric pain with nausea and vomiting usually lasted two or three hours, and residual soreness persisted for several days. Eighteen months before admission, the attacks became more frequent. They were more severe, pain was referred to the right shoulder and back, and slight jaundice was occasionally observed afterward. Abdominal distention was noticed several months before admission.

The skin was yellowish and sallow, and there was definite icteric staining in the sclerotics. The abdomen was distended and contained a moderate amount of fluid. The liver and spleen were not palpable. A roentgenogram of the gallbladder area showed multiple stones. The urine was normal. The serum bilirubin was 4.3 mg with a direct van den Bergh reaction. There was retention of phenoltetrachlorophthalein with a reading of 17 per cent.

A Talma-Morison type of omentopexy was performed on September 8. Several liters of ascitic fluid were removed at the time. The liver was small and was described by the surgeon as cirrhotic. The gallbladder contained stones. The patient did not gain strength following the operation. The ascites recurred, hydrothorax developed later and death occurred on September 12.

At necropsy, marked cirrhosis with ascites was found. The liver weighed 948 Gm. The gallbladder contained multiple stones. The appearance of the patient, the ascites and the small shrunken liver were almost similar to these observations in case 4 (case 13, table 1). The long history of attacks of gallstone colic, however, serves to classify this case as one in which biliary obstruction and infection predominated.

CASE 9 (case 50, table 3) —*Biliary Cirrhosis without Extrahepatic Obstruction but with Ascites*. A man, aged 51, first came to the Mayo Clinic in March 1923, because of diarrhea and a mass in the upper left quadrant of the abdomen. He had had typhoid fever as a child. At the age of 25 he visited Cuba, where he was reported to have had malaria and yellow fever. In 1917 and at irregular periods thereafter, he suffered from severe diarrhea, with bloody mucoid stools. Examination in 1917 revealed slight jaundice and enlargement of the spleen. The gallbladder was drained surgically, and the jaundice disappeared temporarily, the diarrhea persisted.

When first examined the spleen was greatly enlarged and extended nearly to the umbilicus. The stools contained blood, and proctoscopic examination showed the presence of hemorrhagic proctitis. The urine was normal, and the patient was not anemic. Rectal irrigations and the administration of emetine caused partial relief from the intestinal condition.

The patient did not gain strength, however, periods of slight painless jaundice of several days' duration became progressively more frequent, and finally the jaundice became permanent, although it fluctuated in degree and was never marked. Ascites developed a month before his return on Dec 3, 1924. At that time there was a brownish pigmentation of the skin in addition to slight icterus. The abdomen was distended with fluid, and the superficial veins were prominent. The spleen was greatly enlarged and extended 10 cm below the costal margin. The edge of the liver was felt 8 cm below the costal margin.

Bile pigments were demonstrated in both the urine and the stools. Moderate anemia secondary in type had developed, the erythrocytes numbered 3,650,000, the

leukocytes 4,600, and the hemoglobin was 59 per cent. The serum bilirubin varied from 2.5 to 5 mg. with a direct van den Bergh reaction. The retention of dye was 27 per cent.

The patient responded fairly well to treatment with merbaphen for a while, and the ascites partially disappeared. He returned home, but later began to fail, lost a little weight, became weak and drowsy and died in coma on Jan. 30, 1924. Necropsy was not performed.

Exact diagnosis in a case such as this is impossible without microscopic examination. The history of previous infection, the splenomegaly and the recurrent attacks of painless jaundice, which eventually became permanent, and the terminal coma permit one with assurance to make a clinical diagnosis of biliary cirrhosis of the nonobstructive type.

The ascites in the later stages is probably evidence of secondary interference with the portal circulation similar in origin to that seen in some cases of obstructive biliary cirrhosis. The development of marked ascites and an extensive collateral circulation within the abdomen likewise has been a feature of the terminal condition in dogs subsequent to ligation of the common bile duct.

COMMENT ON INDIVIDUAL TESTS

Fructose Tolerance—In 1914, Rowntree, Marshall and Chesney¹⁴ among others, pointed out the unsatisfactory character of the fructose tolerance test of Strauss in cases of cirrhosis. We have not found the study of the blood sugar curve according to the method of MacLean and de Wesselow¹⁵ to increase the clinical value of the test. Ligation of the common duct in animals produces a progressive decrease in the fructose tolerance. In patients with obstructive jaundice, a greater number of positive tests were obtained than in normal persons, but the results were difficult to interpret. Similar results were obtained in the different varieties of cirrhosis. Two positive and two doubtful tests were obtained in a total of nine cases of portal cirrhosis, while two positive and three doubtful tests were obtained in a total of eight cases of biliary cirrhosis. As in the cases of obstructive jaundice, this proportion is not sufficiently great to make the test of diagnostic value in any individual case. There was apparently no significant disturbance of the fasting blood sugar level in any of the cases studied.

NITROGEN PARTITION OF THE BLOOD

Bollman, Mann and Magath¹⁶ have reemphasized the importance of the liver in the formation of urea within the body. The blood urea

¹⁴ Rowntree, L. G., Marshall, E. K., and Chesney, A. M. *Studies in Liver Function*, *Tr. A. Am. Phys.* **29**: 586, 1914.

¹⁵ MacLean, H., and Wesselow, O. L. V. *The Estimation of Sugar Tolerance*, *Quart. J. Med.* **14**: 103, 1920-1921.

¹⁶ Bollman, J. L., Mann, F. C., and Magath, T. B. *Studies on the Physiology of the Liver*. VIII. *Effect of Total Removal of the Liver on the Formation of Urea*, *Am. J. Physiol.* **69**: 371, 1924.

level may be low in portal cirrhosis, in one case 9 mg, an observation in accord with the previous report of Rowntree, Marshall and Chesney. There is a decrease in the blood urea in dogs when the common bile duct is obstructed experimentally, and there is a tendency for the blood urea of patients with obstructive jaundice to fall within the lower limits of the normal. A similar change is observed in the present series of cases of biliary cirrhosis. The urea values observed in either type of cirrhosis are for the most part within the lower limits of normal. In view of the accompanying nutritional disturbance in so many of these cases, it is doubtful whether much diagnostic importance can be attached to these changes in the nitrogen partition of the blood. Furthermore, the terminal rise in blood urea observed in case 4 (case 13, table 1) is evidence that urea formation is by no means in complete abeyance. In consequence, we do not feel that changes in the nitrogen partition of the blood with a reduction in the proportion of urea are of great diagnostic import in the individual case.

The other nitrogenous constituents of the blood that were studied namely, the total nonprotein nitrogen and the uric acid, creatinine and amino-acid nitrogen, did not show consistent variation from the normal.

Fibrinolytic Ferment—Goodpasture¹⁷ described the presence of a fibrinolytic ferment in the blood in cases of cirrhosis. Rowntree, Marshall and Chesney confirmed this observation. We have not observed fibrinolysis in any other condition, and even in cirrhosis it is relatively infrequent. A positive test is perhaps diagnostic, but a negative test will not permit the exclusion of cirrhosis.

Serum Bilirubin—The serum bilirubin was normal in amount in the majority of the cases of portal cirrhosis with ascites. The finding of a slight increase in the bilirubin in five instances, however, is in accord with the clinical observation that slight and transient jaundice not infrequently accompanies this form of cirrhosis. With the occurrence of frank jaundice in the terminal stages of this condition, the serum bilirubin becomes elevated (chart 1).

Biliary cirrhosis, whether of the obstructive or nonobstructive type, is usually accompanied by an increase in the serum bilirubin. This increase in general is moderate or slight, and comparable with the subicteric hue of the skin. The direct van den Bergh reaction was obtained in all the cases that showed an increase in the quantity of serum pigment. The degree of retention of pigment in these cases in general did not reach the high level seen in jaundice due to gross obstruction of the extrahepatic bile ducts. Moreover, it seemed to be largely

17 Goodpasture, E. W. Fibrinolysis in Chronic Hepatic Insufficiency, *Bull. Johns Hopkins Hosp.* **25** 330, 1914.

It is difficult to explain fully the changes observed in the phenoltetrachlorophthalein test. The degree of retention of dye is greater in the presence of ascites. On the other hand, relief from the ascites did not affect the degree of retention in the majority of instances. The test in these cases is apparently independent both of the degree of interference with the portal circulation and of disturbances in the excretion of bile. It most closely corresponds to the extent of the degenerative processes in the liver, and, while it may be modified by regeneration, it is possible that the areas of regenerated hepatic cells are functionally less efficient than normal. This would explain in part the slight effects noted in relation to the size of the liver.

Following the experimental production of biliary obstruction, there is a close parallelism in the changes in the phenoltetrachlorophthalein test and the increase in the serum bilirubin. Similarly, there is a correspondence between the increase in the serum bilirubin and the degree

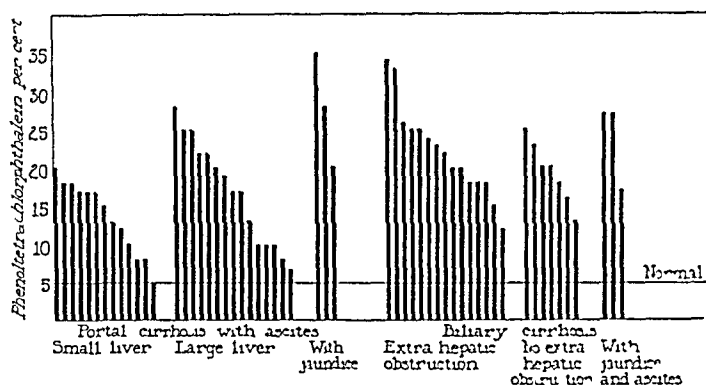


Chart 2—Variations in the degree of phenoltetrachlorophthalein retention in different types of hepatic cirrhosis, the maximum normal level is indicated

of retention of dye observed in cases of obstructive jaundice. In cases of biliary cirrhosis, retention of phenoltetrachlorophthalein uniformly occurred. It was more marked in this condition than in the cases of portal cirrhosis, an observation which may be related to the degree of retention of bile. At the same time we wish to point out that the degree of retention of dye is relatively greater than one would expect to find in a case of obstructive jaundice having the same degree of bilirubinemia. This disproportion between the serum bilirubin and the phenoltetrachlorophthalein we believe to be evidence of the marked changes present in the liver. As such it may have clinical significance.

COMMENT

We have reported a series of cases of chronic hepatitis with inflammatory and proliferative changes of the type usually described under the head of cirrhosis. From the clinical point of view a detailed discussion

of the classification of such cases seems unwise at the present time, for intermediate and mixed forms occur, particularly in the terminal stages of the process, however, the presence or absence of ascites and jaundice and their sequence may serve for tentative division of cases into those of portal and biliary cirrhosis, respectively

Functional tests may be taken as further evidence of the validity of this differentiation. In common with our experience in other hepatic conditions we have found it difficult to demonstrate consistently changes in the metabolic functions of the liver, with particular reference to changes in carbohydrate or protein metabolism. The most striking changes have been those shown by the use of phenoltetrachlorophthalein.

In advanced cirrhosis of either type, marked retention of dye occurred without reference to the presence of jaundice or ascites. In portal cirrhosis the striking functional observation is the high degree of retention in the absence of bilirubinemia. This evidence of dissociation of function is characteristic, similar changes have been observed previously by us in carcinomatous involvement of the liver without icterus. The degree of retention of dye in this series of cases of portal cirrhosis roughly corresponded to the degree of supposed hepatic damage, being slight in those cases without ascites which presumably were representative of an early stage of cirrhosis with minimal disturbance of hepatic function. At the same time, a direct relationship was not observed between the degree of retention of dye and the degree of ascites present. Furthermore, the complete disappearance of ascites is not accompanied by disappearance of the retention, and we feel that the circulatory disturbance responsible for the ascites is not of itself an index of the degree of functional damage to the liver. It is possible that the phenoltetrachlorophthalein test in cirrhosis is indicative of the functional hepatic damage and in a sense the balance between the degenerative and regenerative processes in the liver. It is of interest in this connection to note the decrease in the degree of retention of dye coincident with the clinical improvement in cases 1 (case 4, table 1) and 3 (case 17, table 2) in which medical treatment was instituted. At the same time, one must recognize that a definite relationship could not be found between the exact degree of retention of dye and the size of the liver.

In biliary cirrhosis, whether of the obstructive or nonobstructive type, the serum bilirubin was uniformly increased. This increase in general was slight, corresponding to the mild degree of chronic jaundice present in such cases. Extreme degrees of bilirubinemia such as occur in the so-called catarrhal jaundice or in some cases of malignant obstruction of the common duct were not seen. As in such cases, however, a direct van den Bergh reaction was present in all cases of biliary cirrhosis.

The phenoltetrachlorophthalein test is perhaps of less diagnostic significance in biliary cirrhosis because of the associated retention of bile. On the other hand, the degree of retention of dye is greater than ordinarily expected on the basis of the increase in the serum bilirubin. This disproportion apparently is related to the permanent changes in the liver and so may have some diagnostic value.

ANALOGY BETWEEN CERTAIN TYPES OF RENAL AND HEPATIC DISEASES

An analogy may well be drawn between abnormal conditions in the liver and those observed in the kidney. In cases of pyelitis or pyelonephritis there is an infection, which perhaps is primary in the pelvis, but which later spreads to the renal tissue proper. In consequence of the long continued infection and the intermittent obstruction, the parenchyma is destroyed and replaced by fibrous tissue, and a secondarily contracted kidney is ultimately produced. In chronic glomerulonephritis, on the other hand, there is evidence of repeated injury to the renal parenchyma by toxic or infectious agents. An inflammatory reaction with deposition of fibrous tissue follows, the epithelial degeneration leading in time to the formation of a contracted kidney. In arteriosclerotic or vascular disease of the kidney the interference with the renal circulation produces areas of malnutrition with consequent atrophy and scarring. This, too, leads to the development of a contracted kidney. In each instance laboratory evidence of functional disturbances indicates the severity of the process and confirms the clinical symptoms of renal insufficiency.

The gross appearance of some of these different types of contracted kidney may be similar, especially in the late stages. The functional changes are similar in all. If, as frequently occurs, a mixed or combined type of nephritis is present, it becomes difficult on pathologic evidence alone to determine the primary lesion, although this point may be clarified by clinical evidence, particularly concerning the chronologic sequence of events.

Obviously, care should be used in making an analogy between the diseases of these two organs and especially as regards the deductions drawn therefrom, nevertheless there are certain points of similarity. In this manner, it is evident that the pathologic processes responsible for obstructive biliary cirrhosis resemble those seen in chronic pyelitis or chronic pyelonephritis. The nonobstructive type of biliary cirrhosis and portal cirrhosis may be compared with chronic glomerulonephritis and the arteriosclerotic kidney, respectively. The cases of cirrhosis with terminal ascites and jaundice correspond roughly to the end-stage or contracted kidney. Combined or mixed forms of cirrhosis occur as do combined or mixed forms of nephritis.

In this terminal stage of cirrhosis, differentiation on clinical, functional or pathologic grounds may be impossible, and the nature of the initial process must be presumed largely from the history

SUMMARY

We are impressed with the fact that the condition termed cirrhosis of the liver is an end-result of chronic inflammatory, degenerative and proliferative changes that may be produced by a variety of disease processes. The determination of the concentration of bilirubin in the serum and of the retention of phenoltetrachlorophthalein promises to be of assistance in the clinical study of such cases. The other tests of hepatic function studied have served to emphasize the importance of the great functional reserve of the liver. They failed, however, to show significant or sufficiently specific changes to make them of any great clinical value.

The phenoltetrachlorophthalein test is of particular value in the diagnosis and study of cases of portal cirrhosis with ascites. In such cases it is apparently an index to the existing functional balance between degenerative and reparative changes in the liver. As such, the observations are largely independent of the amount of ascitic fluid. One case is reported in which there was some evidence of improvement clinically and functionally and in which regenerative changes in the liver during treatment were assumed.

While jaundice is not a striking manifestation in portal cirrhosis, the study of the serum bilirubin showed the presence of latent icterus in several instances.

The study of the serum bilirubin has been of particular value in determining the degree of retention of bile in all types of biliary cirrhosis. Retention of dye is uniformly present but is more marked than would usually be expected from the degree of bilirubinemia. This disproportion is perhaps evidence of the pathologic changes in the liver.

In the end-stages of cirrhosis, irrespective of whether it is primarily portal or biliary in origin, the clinical picture and pathologic and functional changes may be well-nigh indistinguishable. Diagnostic differentiation is then based on the chronologic sequence of the more remote events as elicited in the history.

In cirrhosis of the liver functional studies are proving of considerable clinical importance, particularly from the standpoint of classification and differential diagnosis. They stimulate more serious clinical investigation and emphasize the need of focusing the attention of physicians on the problems of hepatic disease.

BLOOD SUGAR

COMPARISON OF BLOOD SUGAR CURVES FOLLOWING INGESTION AND INTRAVENOUS INJECTION OF GLUCOSE[†]

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WITH THE ASSISTANCE OF

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The degree of hyperglycemia that follows the administration of glucose is commonly used as a measure of the efficiency of the sugar-utilizing mechanism of the body. The method ordinarily employed in performing this test is to measure the concentration of sugar in the blood at intervals after the ingestion of a certain amount of glucose. The criticism has long been made that the speed with which glucose is absorbed from the intestinal tract may vary. For example, Beeler and others¹ have demonstrated that an hour after the ingestion of glucose, from 22 to 68 per cent may be aspirated from the stomach. The amount may vary in different persons and in the same person from time to time. However, they fail to show that the amount of glucose recovered is inversely related to the height of glycemia. It is well known, on the contrary, that the ingestion of varying amounts of sugar above 50 Gm or so makes little difference in the degree of the resulting hyperglycemia. Nevertheless, some workers prefer to administer the glucose by intravenous injection. Previous work on this subject has been adequately reviewed by Rigler and Ulrich,² and Jorgenson.³ The essential difference between the two methods is that glucose given by mouth passes first through the liver, which it does not if introduced parenterally. We have seen no report concerning the use of both methods in the same subjects.

In the course of an investigation of the carbohydrate metabolism of persons subject to recurring convulsions,[†] we had occasion to employ

* From the Laboratory of the Department of Neuropathology, Harvard Medical School and the Medical Service of the Massachusetts General Hospital.

[†] This research was made possible through a grant by the Committee on Epilepsy, New York City.

1 Beeler, C., Bryan, A. W., Cathcart, E. P., and Fitz, R. An Improved Alimentary Glucose Tolerance Test, *J. M. Research* **1** 549, 1922.

2 Rigler, L. G., and Ulrich, H. L. Blood Sugar Reaction Following Intravenous Injection of Glucose, *Arch. Int. Med.* **32** 343 (Sept.) 1923.

3 Jorgensen, S. Comparison Between the Intravenous and Oral Application of Glucose for Loading of the Carbohydrate Metabolism, *Acta Med. Scandinav.* **55** 116, 1926.

4 Lennox, W. G., O'Connor, M., and Bellinger, M. Studies of the Metabolism in Epilepsy. III. The Blood Sugar Curve, *Arch. Neurol. & Psychiat.*, to be published.

both methods in a large group of subjects. Because the comparative results obtained seemed to bear little relationship to epilepsy, they are presented here. This paper deals with 100 subjects whose blood sugar curves were drawn following both oral and intravenous administration of glucose. In all, 325 curves were made, 175 following ingestion and 150 following intravenous injection of glucose.

MATERIAL AND METHODS

Nine of the subjects were healthy men students. The rest, with a few exceptions, were patients with so-called epilepsy. None had diabetes. The tests were performed in the morning. Five cubic centimeters of venous blood were drawn from each subject when fasting, and at intervals of one-half, one and two hours after the administration of glucose. Specimens of urine were collected at the end of the two hour period. An amount of pure dextrose equal to 1.5 Gm. per kilogram of body weight in 33 per cent solution was ingested. For the injection tests, we used an amount of chemically pure anhydrous dextrose equal to 0.33 Gm. per kilogram of body weight in 20 per cent watery solution. In a few instances we buffered the glucose solution as recommended by Stoddard.⁵ Because we feared that the injection of phosphate might modify results, and also because, in one instance, reaction occurred even with this solution, we discontinued its use. We followed the method of injection described by Rigler and Ulrich,² except that a syringe and three-way stop-cock were substituted for the pressure flask. Glucose was injected at the rate of 4 Gm. (20 cc. of solution) per minute. The average period of injection was approximately five minutes. In addition to the previously mentioned samples, blood was collected four minutes after the injection. Initial curves by the two methods were approximately equal in number. Reactions occurred in a little more than 5 per cent of the tests. On a given day, a reaction would occur in only one of several subjects, all of whom received the same material. Although many of the subjects received repeated injections, none had more than one reaction. The use of freshly distilled water, of old rubber tubing or of buffered solution did not prevent the appearance of an occasional reaction. The blood sugar curve of patients who had reactions was neither markedly abnormal nor markedly different from other curves made when no reaction occurred.

Blood sugar was measured by the method of Folin and Wu,⁶ using the sugar tubes described by Evans,⁷ and urine sugar by the method of Benedict, as recommended by Smith.⁸ For the sake of brevity, we shall speak of blood sugar curves following ingestion and intravenous injection of glucose as ingestion curves and injection curves, respectively.

RESULTS OBTAINED

In table 1 we present intravenous curves of eleven healthy subjects, for nine of whom ingestion curves also were drawn. Two of us served as normal controls, the other subjects were medical students who had had recent physical examinations. So far as we are aware, there are no

5 Stoddard, J. L. The Avoidance of Intravenous Glucose Reactions, Boston M. & S. J. **191** 1121 (Dec. 11) 1924.

6 Folin and Wu, H. A System of Blood Analysis. A Simplified and Improved Method for Determination of Sugar, J. Biol. Chem. **41** 367, 1920.

7 Rothberg, V. E., and Evans, F. A. A Modified Folin and Wu Blood Sugar Method, J. Biol. Chem. **53** 443 (Dec.) 1923.

8 Smith, M. A Micro-Modification of the Method of Benedict for the Quantitative Determination of Reducing Sugar in Urine, J. Lab. & Clin. Med. **7** 3 (March) 1922.

published measurements of sugar curves from known normal subjects following intravenous injection of an amount of glucose similar to that used in these experiments. The seven nondiabetic patients whom Rigler and Ulrich² used were mostly subjects from whom abnormal reactions were to be anticipated (patients with hypertension, arthritis, cancer or of advanced age). The blood sugar had reached the fasting level in these patients by the end of two hours. Jorgensen and Plum⁹ and Jorgensen³ injected 20 Gm of glucose dissolved in 50 cc of water in their subjects and drew capillary blood for examination at frequent intervals. In their

TABLE 1—*Blood Sugar Curves of Healthy Subjects Following Injection and Ingestion of Glucose*

Subject	Amount Glucose Given, Gm	Blood Sugar, Mg per 100 Cc Blood							Index Number	Urine Sugar, Gm
		Fast	Minutes After Glucose Injected							
			4	15	30	60	90	120		
1	23.3*	86	243		123	75		75	1.16	0.43
2	18.8	104	248	155	126	91	83	94	1.06	0.37
3	20.4	101	200	175	145	77	72	91	1.17	0.23
4	20.4	105	190	176	146	120	110	98	1.10	0.46
5	16.3	100	205	109	89		99	91	0.92	0.54
6	19.4	98	211	165	136	100		105	1.23	0.44
7	24.8	97	244	74	66	84	99	105	0.88	0.52
8	21.2	124	224	200	169	119	122	105	1.10	0.27
9	21.0	88	240	144	90	78				8.8
10	28.0	87	208	174	114	84	100	93	1.2	0.12
11	16.6	80	216		83	83		82	1.03	0.33
1	102.9†	103			167	116		83	1.21	0.15
2	84.8	116		126	132	143		133	1.19	0.13
3	91.8	112			133	164		140	1.36	0.30
4	91.8	110			133	119	110	100	1.06	0.13
5	81.6	99		108	133	78	87	80	1.08	0.05
6	97.2	102		130	165	116	108	102	1.31	0
7	111.6	101		133	100	100	76	109	1.08	0
8	95.3	128		213	239	132	143	138	1.47	0.14
9	46.2	105		116	102	133	85			0.24
Average injection	20.6	100	223	149	121	93	95	96	1.08	1.34
Average ingestion	89.2	108		138	145	122	111	111	1.22	0.13

* One third gram per kilogram of glucose injected intravenously.

† One and five-tenths grams per kilogram of glucose ingested, except in subject 9 who received 0.75 Gm per kilogram.

The measurements for subject 1 are the average of four intravenous and six ingestion curves, and for subject 2 the average of two intravenous and two ingestion curves.

The average values are for the first nine subjects. Missing 60 and 90 minute values are supplied by interpolation.

two published reports they tabulate observations on thirty-two non-diabetic patients, most of whom had no disease condition that might in itself give an abnormal blood sugar curve. In all but six of their patients, the blood sugar had returned to normal within ninety minutes.

Blood from our normal subjects was taken four, fifteen, thirty, sixty, ninety and 120 minutes after the injection of glucose. Blood sugar returned to the fasting level as follows: in fifteen minutes, one subject, in thirty minutes, three subjects, in one hour, six subjects and in two

⁹ Jorgensen, S, and Plum, T. Differential Diagnosis Between Benign and Malignant Glycosuria by Means of Intravenous Injections of Small Quantities of Grape Sugar, *Acta med Scandinav* 58:161 (May 22) 1923.

hours, one subject. Though our group of normal controls is small, we are forced to use it as a standard for judging the measurements from the larger group of patients. Chart 1 shows the average ingestion and injection curves of these nine subjects. It will be seen that although the glucose injected was but 24 per cent of the amount ingested, the peak of the average injection curve is much the higher. However, after the first precipitous fall of the injection curve, the two curves run a nearly parallel course.

Comparison of the injection and ingestion curves of each subject shows substantial agreement between the two methods. For example, both curves of subject 7 show that there was a remarkably quick disposal of sugar. Fifteen minutes after injection and thirty minutes after ingestion of glucose, the blood sugar was below the fasting level.

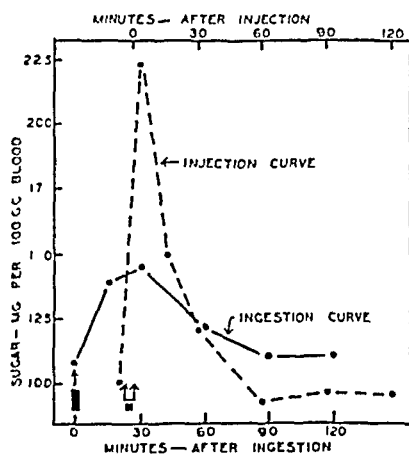


Chart 1—The average blood sugar curves following the ingestion of 89 Gm of glucose and the injection of 20 Gm of glucose in the same nine healthy subjects (data from table 1). Ordinate represents milligrams of glucose per hundred cubic centimeters of whole blood. Abscissa represents minutes after administration of glucose. The two curves are placed so that their peaks correspond.

The data obtained from the whole number of subjects are too numerous to permit presentation in detail. For the purpose of comparison, we have endeavored to express the height of each blood sugar curve by a number. This figure, which we shall speak of as the index number, was obtained for ingestion experiments by adding the highest and the two hour measurements of blood sugar and dividing by two times the fasting value. In the case of intravenous tests, we feared that the sugar content of the blood drawn at four minutes might show variation because of incomplete mixing or because of the rapidly diminishing concentration of glucose, and used the half hour value as the highest. In several instances we were not able to calculate the index numbers of curves because two hour measurements were lacking. In charts 2 and 3 we have plotted the index numbers of the intravenous and the ingestion curves.

against each other. In these charts, if the height of curves obtained by these two methods were proportional, the dots would fall in a zone extending from the lower left corner to the upper right corner of the chart.

Chart 2 presents the results obtained by plotting the index numbers of individual ingestion and injection curves against each other. Measurements of healthy subjects are represented by crosses, of patients on whom a single test by each method was made, by solid dots, and of those on whom repeated tests were made by circles. In the last group, the first injection curve of a subject was plotted against his first ingestion curve, the second injection curve against his second ingestion curve, etc. In seeking to obtain a standard of normal correlation of these index numbers, we drew a square in charts 2 and 3 which includes seven of the nine measurements from healthy persons listed

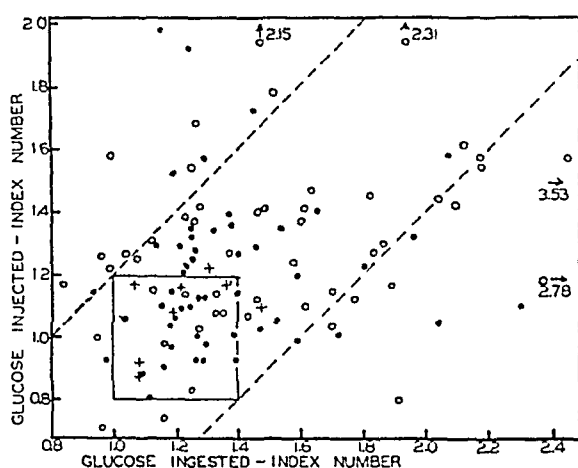


Chart 2—Comparison of 115 measurements in which the height of ingestion and injection curves was compared. Ordinate represents the height of injection curves and abscissa the height of ingestion curves, as indicated by an index number. The index numbers were obtained by adding the highest value and the two hour value of curves and dividing by twice the fasting value. In the injection curves the half hour value was used in place of the highest. Crosses represent normal controls. Dots represent measurements of subjects on whom only one test was performed, whereas circles represent measurements of subjects on whom two or more tests by both methods were performed. The large square indicates limits of normal and the zone between broken lines the area in which there is correspondence between height of ingestion and injection curves.

in table 1. Of the remaining two, the ingestion curve of subject 9 was not strictly normal, and because the hypoglycemia that existed at the end of the first hour was not taken into account, the injection curve of subject 7 was really lower than the index number would indicate. The blood sugar curves represented by the limits of this square are within rather strict limits of normal. The parallel dotted lines extending from the corners of the square define a zone, values within which show some proportionality in the degree of hyperglycemia following ingestion and

injection of glucose. Inspection of chart 2 shows a wide scattering of the dots and circles. However, of the 115 measurements, eighty-six or 75 per cent are within the zone that we have marked as normal. Measurements of patients on whom repeated tests were made were more scattered than measurements of those on whom but a single test was made, probably owing to the fact that tests were repeated more frequently on patients who presented abnormal initial results.

As has been stated, most of these measurements were made on persons subject to convulsions. As noted in a previous paper,¹ the blood sugar curves of many of these patients presented abnormal variation in the level and configuration of successive curves. For this reason, it is probable that the measurements represented in chart 2 show a more widespread scattering than would measurements of patients whose physiologic functions were more stable. Some of this variability can be neutralized by taking the average of several curves rather than individual curves. This has been done in chart 3, which represents average

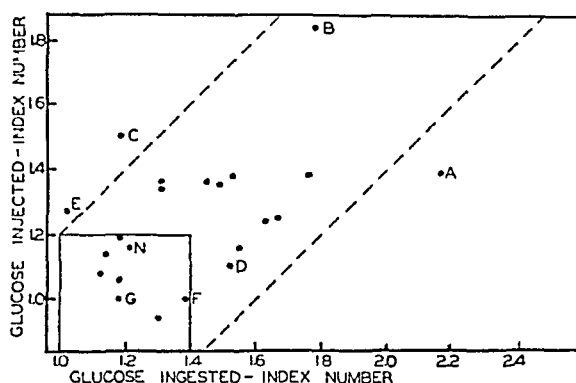


Chart 3—Comparison of the average height of blood sugar curves (as represented by their index numbers) from twenty-two subjects on whom two or more tests by both methods were performed. The letters indicate the subjects whose blood sugar curves were presented in figure 4. *N* is a normal subject, the others are patients.

measurements of the twenty-two subjects on whom two or more blood sugar tests were made by each method. Of these twenty-two, nineteen or 87 per cent are within the normal zone. Therefore, in this group of nondiabetic patients, many of whom reacted to the administration of glucose in an abnormal manner, there is a fairly normal degree of proportionality in the height of blood sugar curves following ingestion and injection of glucose.

In order to visualize more clearly the differences shown in some of these subjects, chart 4 presents the average curves of eight of the subjects whose measurements are on the periphery of the group shown in chart 3. The letters placed near the dots in chart 3 indicate subjects whose curves are represented in chart 4. The curves lettered *N* represent the average of six ingestion and four intravenous curves of one of

us *A* represents the one extreme example of a patient whose average ingestion curve was disproportionately higher than her average injection curve. The average injection curve, judged by the curves of normal subjects in table 1, was slightly elevated, whereas her average ingestion curve was clearly diabetic in type. She showed no symptoms of diabetes except a gain of 28 pounds (12.7 Kg) in weight during the twenty months of observation. In contrast with this is case *B*. Her average ingestion curve, though abnormally high, was lower than that of *A*, but during the first half hour following the injection of glucose there was distinct delay in the removal of glucose from the blood. Although this patient had no symptoms of diabetes, there was a family history of disturbance of the endocrine glands, namely, a sister had died of diabetes, her mother had exophthalmic goiter, and a brother had myxedema. Patients *C* and *E* had low ingestion curves and moderately

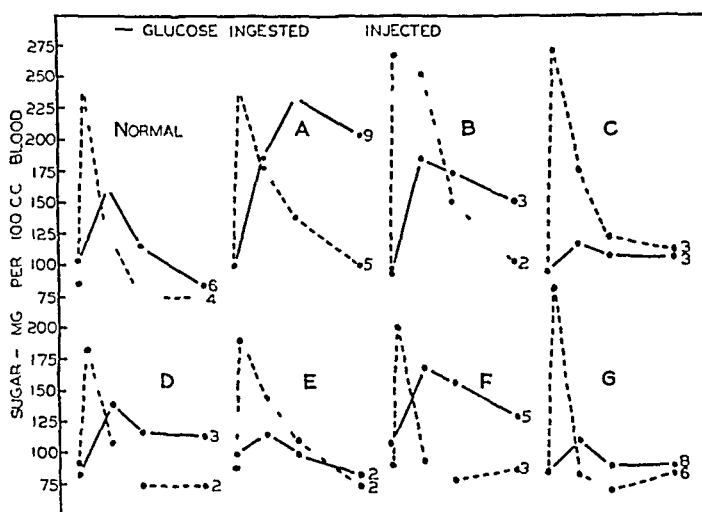


Chart 4—Average ingestion and injection blood sugar curves of eight subjects, the index numbers of whose curves are compared in chart 3. The numbers accompanying each curve indicate the number of tests which were performed by each method. The curves drawn are the average of these separate curves.

elevated injection curves. Case *G* had curves which were low and exactly proportional. Regarding the several subjects in whom there was a discrepancy between the height of ingestion curves and of injection curves, we do not know the cause of this discrepancy or which of the two methods gages the efficiency of the sugar regulating mechanism more correctly.

Chart 5 is given as an example of the fact that both ingestion and injection curves may give intermittent evidence of delay in the removal of glucose from the blood. The figure records five ingestion and four injection curves of a patient who had essential hypertension and epilepsy. In the first two ingestion curves, numbered 1 and 5, the concentration of blood sugar at one hour was much greater than at one-half hour.

Two of the injection curves also, numbered 3 and 4, showed similar delay. For thirty minutes after the injection, the concentration of glucose in the blood remained stationary. Five other curves of this subject were not markedly abnormal.

The question next arises concerning the degree of dispersion of values obtained in a group of subjects tested by the two methods. Jorgensen³ has compared his curves drawn for nondiabetic patients following intravenous injection of 20 Gm of glucose with Hagedorn's¹⁰ curves from normal subjects following ingestion of 1 Gm of glucose per kilogram of body weight. Jorgensen's curves show 20 per cent deviation from the mean against a 39 per cent deviation for those of Hagedorn. This comparison is open to criticism because one observer used patients and the other used normal subjects. Our observations are free from this objection because the same subjects were used for both tests.

Chart 6 represents the comparative frequency of ingestion and injection curves of various heights in our group of 100 subjects. Index

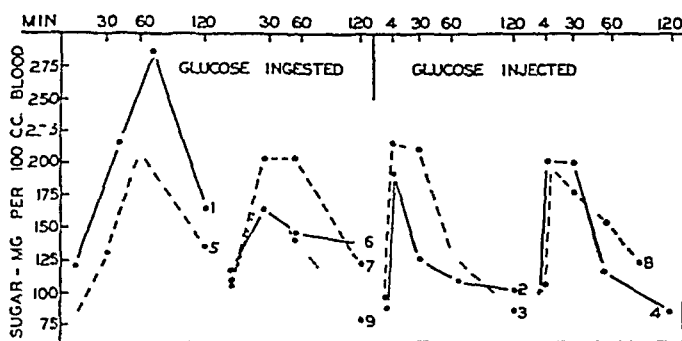


Chart 5—Five injection and four ingestion curves of a patient with essential hypertension and epilepsy made during a period of twenty months. Certain curves by each method show initial delay in the removal of sugar from the blood. The numbers indicate the order in which the tests were performed.

numbers of 122 injection and 154 ingestion curves are plotted. Because our method of computing index numbers is arbitrary, the two curves are placed so that their apexes coincide. It will be seen that the distribution of normal curves (those with index numbers of 16 or below) is much alike for the two methods. However, the proportion of curves with index numbers above 16 is 18.5 per cent for ingestion and 5.6 per cent for injection curves. This indicates that the ingestion method gives a greater proportion of higher curves. We have pointed out elsewhere¹¹ that the difference between successive curves was less for injection than for ingestion curves. Injection tests did not give so many curves that were high only on initial trial. This smaller degree of variation in results

¹⁰ Hagedorn, H. C. *Undersøgelser vedrørende blodsukkerregulationen hos mennesket*, Thesis, Copenhagen, 1921.

¹¹ Lennox, W. G., and Bellinger, M. *Repeated Blood Sugar Curves in Nondiabetic Subjects*, to be published.

obtained by intravenous injection of glucose may be due, of course, to the much smaller amount of glucose used in the intravenous tests. In another article¹² we made a comparison of duplicate curves following ingestion and injection of the same amounts of glucose.

RENAL THRESHOLD

The older literature dealing with glycosuria following intravenous injections of glucose has been reviewed by Allen¹³ and Kleiner¹⁴. Various authors have suggested that renal permeability may be altered for glucose which is introduced parenterally. In 1913 Thannhanser and Pfister¹⁵ observed that when glucose was injected intravenously, the assimilation limit was only about 20 Gm. More recently Rosenberg¹⁶ and Varela and Rubino¹⁷ have shown that although glucose given by rectum may result in only a slight increase in blood sugar, glycosuria may occur. We have seen no observations in which results following

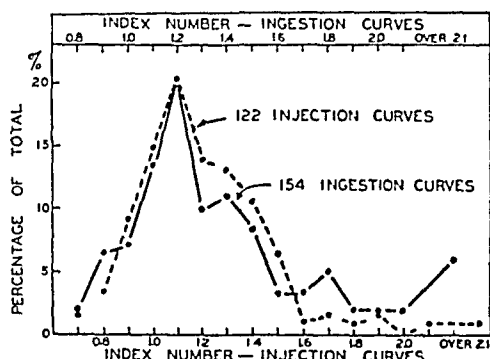


Chart 6—Comparative frequency of various heights of 122 injection and 154 ingestion blood sugar curves. Ordinate represents the percentage of the total number of curves. Abscissa indicates the index numbers of curves. The scales are arranged so that the apexes of the two curves coincide. The two curves are roughly parallel, except that there is an undue proportion of high ingestion curves.

both enteral and parenteral administration of glucose were secured from the same group of subjects.

Table 2 presents the observations regarding the presence or absence of glycosuria in 160 ingestion and 137 injection experiments. There is

12 Lennox, W. G., and Bellinger, M. Stimulation of the Sugar Regulating Mechanism as Shown by Duplicate Blood Sugar Curves, to be published.

13 Allen, F. M. Glycosuria and Diabetes, Harvard University Press, 1913.

14 Kleiner, J. S. The Disappearance of Dextrose from the Blood After Intravenous Injection, *J. Exper. Med.* **23** 509, 1916.

15 Thannhanser, S. J., and Pfister, H. Ueber experimentelle Hyperglykämie beim Menschen durch intravenöse Zuckereinjektion, *München med. Wchnschr.* **9** 2155, 1913.

16 Rosenberg, Max. Ueber die praktische Bedeutung der alimentären Hyperglykämie Kurve, *Klin. Wchnschr.* **1** 360 (Feb. 18) 1922.

17 Varela and Rubino. Rektale Dextrosezufuhr und Blutzucker, *Med. Klin.* **18** 831 (June 25) 1922.

evident contrast between the incidence and degree of glycosuria in the two groups. Thirty-four per cent of the ingestion experiments were associated with glycosuria, against 85 per cent of the injection experiments. Comparison of the total results is hardly fair, however, because concentration of blood sugar in most of the injection curves was above, and in ingestion curves below, 200 mg. However, there is marked contrast in the proportion of subjects showing glycosuria at various levels of blood sugar. In the ingestion tests, the proportion presenting glycosuria decreased as the level of the blood sugar fell. For example, with blood sugar above 200 mg, 59 per cent of these subjects had glycosuria, whereas with the blood sugar below 200 mg, only 30 per cent had glycosuria. In the injection experiments, on the other hand, the elevation of the blood sugar made little difference in the incidence of glycosuria. Above 200 mg the proportion was 87 per cent, below 200 mg, 83 per

TABLE 2—*Proportion of Subjects Showing Glycosuria Following Ingestion and Injection of Glucose*

Highest Blood Sugar, Mg	Glucose Ingested					Glucose Injected				
	Total Mea- sure- ments	No Sugar	Sugar Present			Total Mea- sure- ments	No Sugar	Sugar Present		
			Num- ber	Per Cent	Average Amount, Gm			Num- ber	Per Cent	Average Amount, Gm
More than 250	6	2	4	66	1.26	42	9	33	78	1.31
201 to 250	16	7	9	56	0.39	72	6	66	92	1.10
176 to 200	20	12	8	40	1.27	17	3	14	82	0.80
151 to 175	33	24	9	27	0.25	6	1	5	83	0.83
Less than 150	85	60	25	29	0.28					
Total	100	105	55	34	0.53	137	19	118	85	1.12

cent. Though the amount of glucose excreted was small in both groups, the average amount was twice as much for injection as for ingestion tests, namely, 1.12 Gm. for the former against 0.53 Gm. for the latter.

These differences are more significant when one remembers that in each test nearly five times as much sugar was ingested as was injected, and in the ingestion experiments the high levels reached were maintained for a longer time than in the injection experiments. Again, though in our injection experiments we always obtained blood at or near the peak of the curves, in our ingestion experiments hyperglycemia may have been greater than our measurements, made at half hourly intervals, would indicate.

The more ready excretion of intravenously injected glucose may possibly be explained by the fact that the rate of injection (4 Gm. a minute) presumably was faster than the rate of absorption from the intestines. That a rapid rate of introduction of glucose into the circulation is not necessarily associated with increased glycosuria, is suggested by the experiments presented in table 3. In subject A, 3 Gm. of glucose per kilogram (186 Gm. in all) were injected at the rate of 6 Gm. per

minute, and 11.4 Gm of glucose were excreted. In subject *B* an equal amount of glucose per kilogram (205 Gm in all) was injected at half this rate (or 3 Gm per minute), and 15.1 Gm were excreted. In these experiments the glucose was given in two equal doses. The interval between injections was approximately an hour. In each case glycosuria was greater with the second injection. This is seen more clearly with subject *B*. Although hyperglycemia was not nearly so high after the second injection of glucose, the amount of sugar excreted was twice as great. These two subjects showed little or no glycosuria when an equal amount of glucose (3 Gm per kilogram) was ingested. These observations, though few, suggest that the slower entrance of glucose into the blood stream may not be entirely responsible for the smaller degree of glycosuria which accompanies the ingestion of glucose.

TABLE 3—*Glycosuria with Reference to Duplicate Injections of Large Amounts of Glucose at Different Rates*

Subject	Rate and Period of Injection of Glucose	Period of Collection of Urine, Minutes	Limits of Blood Sugar, Mg	Glucose in Urine, Gm
A	6 Gm per minute for 15 minutes	30	606-150	4.86
	6 Gm per minute for 15 minutes	30	574-95	5.71
		50	95-48	0.84
Total	186 Gm (3 Gm per kilogram)	150	606-48	11.41
B	3 Gm per minute for 35 minutes	45	505-275	4.41
		45	275-71	0.62
	3 Gm per minute for 35 minutes	45	338-215	9.69
		45	215-63	0.38
		10	65-50	0.0
Total	205 Gm (3 Gm per kilogram)	190	505-50	15.10

In the injection experiments summarized in table 2, glucose was injected at the same rate in all, yet there was lack of correlation between the incidence of glycosuria and the elevation of blood sugar. It is possible, as various writers have suggested, that glucose which first passes through the intestines and liver is modified in such a manner that it is less readily excreted than glucose which is introduced directly into the blood stream. In view of these observations, the assumption of Woodyatt and others¹⁸ that the ability of the body to assimilate ingested glucose can be measured by the appearance of glycosuria following its injection, is permissible.

COMMENT

Because none of our subjects had diabetes, the data here presented cover rather a narrow range with regard to the degree of abnormality of the blood sugar curves. So far as we could judge from the use of

18 Woodyatt, R. T., Sansum, W. D., and Wilder, R. M. Prolonged and Accurately Timed Intravenous Injections of Sugar, *J. A. M. A.* **115**: 2067 (Dec. 11) 1915.

the two methods in this group of nondiabetic subjects there was a fairly close agreement between the two in most instances. At any rate, the discrepancies between the two methods were no greater than the variations between successive tests by the same method.

The amounts of glucose that we injected were proportional to the weight, and therefore to the blood volume, of the subjects. If all the glucose were to remain in the blood until four minutes after the injection, the concentration of sugar in the blood would be increased approximately 350 mg per hundred cubic centimeters. For example, the average amount of blood sugar in nine normal subjects would be 450 mg after the injection, instead, it was 223 mg, as shown at the bottom of table 1. Therefore, during the nine minutes which elapsed after the injection was begun approximately one half of the injected glucose had disappeared from the blood. The rate of disappearance during this period varied in different subjects, as may be seen by a comparison of the four minute values in table 2 and in chart 4.

With regard to the comparative usefulness of the two methods, we may summarize the advantages of the intravenous route as follows. This method offers accurate dosage. The injection of 20 Gm of glucose results in as high a blood sugar curve as the ingestion of 100 Gm (chart 1), therefore, the intravenous route is particularly useful when, as in testing diabetic patients, one wishes to administer a minimum amount of glucose. When blood is taken at frequent intervals during the course of the tests, the intravenous curve is much smoother than the ingestion curve. Intravenous curves exhibit less variation from subject to subject, and in the same subject less variation from time to time.

As opposed to these advantages, the intravenous method has the following disadvantages. It requires more time and trouble of the investigator, and subjects those being investigated to an occasional reaction. More serious is the objection that glucose which is injected directly into the blood stream is in the nature of a foreign body. When glucose is injected, glycosuria is more pronounced and not so dependent on renal threshold. Also, as we suggest elsewhere,¹² injected glucose may have a less stimulating effect on carbohydrate metabolism than ingested glucose. These observations suggest that glucose which enters the body by way of the intestines and passes first through the liver is treated in a somewhat different manner from glucose which is introduced directly into the blood stream. A blood sugar curve test following intravenous injection of glucose would, therefore, seem to be less nearly physiologic than one following its ingestion. This consideration is largely theoretical.

If, as our study suggests, there is general correspondence in results obtained by both methods, choice of method is largely a matter of convenience rather than of principle. We believe that from the standpoint

of diagnosis, liberal interpretation of blood sugar curves and repetition of abnormal initial curves is of more importance than the method used

SUMMARY AND CONCLUSIONS

1 We have plotted the blood sugar curves of 100 nondiabetic subjects following both intravenous injection and oral administration of glucose

2 Of 115 curves, drawn by both methods, which could be plotted against each other, there was a normal degree of correlation in approximately 75 per cent. The average curves of twenty-two subjects on whom repeated tests were made by both methods showed normal correlation in 87 per cent.

3 When glucose was injected, glycosuria was more frequent and more pronounced than when glucose was ingested, and bore little relationship to the concentration of sugar in the blood.

4 The comparative advantage of the two methods are discussed.

BLOOD BILIRUBIN

ESTIMATION AND CLINICAL SIGNIFICANCE¹

F S PERKIN, M B (TOR)

ANN ARBOR, MICH

Bilirubin is the most important of the bile pigments, the remaining two, biliverdin and bilicyanin, being oxidation products of bilirubin. It occurs in the blood as an acid and is therefore capable of forming salts differing in properties from the free acid. It is produced as the result of the break-down of the red cells of the blood, this probably occurs in the ramifications of the reticulo-endothelial system and has been shown to be almost entirely extrahepatic¹. The bilirubin so produced is carried in the blood stream as a colloidal suspension and excreted from the liver into the bile passages. Before this excretion occurs, it undergoes a transformation in the liver cells from the form in which it is found in the blood to that in which it appears in the bile. The exact nature of this conversion is a matter of dispute, but the recent work of Collinson and Fowweather² tends to show that it consists of a change of the acid bilirubin into a soluble alkaline salt by union with ammonia. As they point out, it has been demonstrated in connection with dyes used for visualization of the gallbladder that only those which form true solutions are excreted with any degree of rapidity. They advance considerable evidence in support of their theory, which apparently warrants serious consideration.

The quantitative determination of blood bilirubin as a routine laboratory measure is a comparatively recent development. It is based on the van den Bergh reaction for the estimation and recognition of bilirubin in blood serum³. This estimation, on which the majority of figures for blood bilirubin previously noted have been based, was later pointed out by van den Bergh to be far from accurate, frequently as the result of a loss of bilirubin in the albuminous precipitate formed. In cases of a direct or biphasic reaction, this loss is considerable, although not so marked when the reaction is indirect. The technique of Thannhauser and Andersen⁴ has overcome this objection by first mixing the diazo reagent with the test plasma, then adding the alcohol and saturated

*From the Department of Internal Medicine, University of Michigan, and Clinical Laboratories, University Hospital.

1 Mann, F C, Bollman, J L, and Magath, T B. *Am J Physiol* **68** 114, 1924.

2 Collinson, G A, and Fowweather, F S. *Brit M J* **1** 1081, 1926.

3 Van den Bergh and Snapper. *Deutsches Arch f klin Med* **110** 540, 1913.

4 Thannhauser, S J, and Andersen, E. *Deutsches Arch f klin Med* **137** 179, 1921.

ammonium sulphate After shaking and centrifugalizing, the clear alcoholic solution of azobilirubin is on the surface with the ammonium sulphate at the bottom and an intervening layer of white albuminous precipitate McNee⁵ found that this estimation gave results varying from as high as three times that of the original van den Bergh method in blood showing a direct or biphasic reaction, and 25 per cent higher in blood giving indirect reactions Similar results were obtained in our laboratory

A study was undertaken of bilirubin levels in the normal person and in a series of cases in which abnormal results were to be anticipated The method used was essentially that of Thannhauser and Andersen, with some modifications

METHOD

To 2 cc of oxalated plasma is added 2 cc of diazo reagent, freshly prepared After from two to three minutes 5 cc of 95 per cent alcohol and 2 cc of saturated solution of ammonium sulphate are added The solution is centrifugalized after shaking The supernatant fluid is carefully drawn off and compared in a colorimeter, preferably of the Du Bosq type as more accurate, or in a Hellige colorimeter, with the standard solution described in the following The result is multiplied by 4, none of the azobilirubin being dissolved in the ammonium sulphate, and expressed in mg per thousand cubic centimeters of blood

The use of plasma instead of serum obviates to a great extent the occurrence of hemolysis which interferes with the reaction and also gives a cloudy supernatant fluid Even with the use of oxalated blood, early centrifugalizing is advisable, although not absolutely necessary

The standard is made by dissolving 2.161 Gm of anhydrous cobalt sulphate in 100 cc of distilled water The salt must be absolutely anhydrous and chemically pure, and when possible the solution should be checked against pure bilirubin This standard gives a color equivalent to that given by 5 mg of bilirubin per thousand cubic centimeters of blood, which constituted the old van den Bergh "unit" Various strengths of the aforementioned standard may be prepared for convenience in reading higher values of the unknown When dilution of the unknown is necessary, 65 per cent alcohol should be used

This standard is permanent if kept in the dark The advantages over the ethereal solution of iron rhodanate originally used are obvious as regards both accuracy and convenience

The use of this method does not interfere with the determination of the qualitative van den Bergh reaction If on addition of the diazo reagent to the plasma, a reddish violet color appears within thirty seconds, the reaction is direct If the color appears later than this and continues to deepen with a further increase on addition of the alcohol, the reaction should be classed as biphasic If a color does not develop on addition of the diazo reagent, the reaction is, of course, indirect

The direct reaction is given by bilirubin only in the form in which it appears in the bile, that is, in cases of obstructive jaundice There is

5 McNee, J W, and Keefer, C S Brit M J 2 52, 1925

considerable evidence for the assumption that the biphasic reaction seen in aisenical jaundice, catarrhal jaundice and other cases of toxic or infective liver disease is the result of damage to the excreting cells of the liver, so-called hepatitis. The interpretation of the biphasic reaction, however, must be absolutely clear to avoid error, as reactions simulating the biphasic are given in cases of obstructive jaundice in which the patients are recovering. In cases in which an indirect reaction alone is obtained, all the bilirubin present is the result of hemolysis, in a normal or abnormal degree.

NORMAL VALUES

With the object of definitely determining the normal range using this method, the blood of fifty presumably normal persons, medical students, interns and others was examined. With one exception, the highest reading was 3.5 mg, the lowest 0.5 mg. Eight showed less than 1 mg, twenty-nine between 1 and 2 mg and twelve 2 mg and over. The one exception had a bilirubin of 7.5 and 8.5 mg on two occasions some weeks apart. He was born in India, and he had never been found to have jaundice on clinical examination. The blood counts, smear and other laboratory tests did not show anything of note, the fragility test showed hemolysis commencing at 0.44 per cent and complete at 0.32 per cent. The liver was somewhat enlarged, and the case was probably one of chronic hepatitis.

Race and sex did not have any apparent influence, four negroes, two Orientals, and representatives of various other races being included in the series. The influence of pigmentation was not so marked as I had been led to expect, but definite brunettes tended to give slightly higher values. Blonds averaged 1.2 mg, the intermediate group 1.3 mg and brunettes 1.8 mg.

Repeated readings on the same person at intervals of several days gave results that did not vary more than a small fraction of a milligram. The effect of diet was not marked, although the observation that fasting specimens gave slightly higher value was confirmed.⁶

Analogous to this, and contrary to the statement that⁷ ingestion of carbohydrate tends to increase the bilirubin content, was the finding in determinations made on patients undergoing glucose tolerance tests. A decrease in bilirubin averaging 0.5 mg occurred in practically every case, as a rule in the second hour specimen, seldom in the first hour specimen. The method of performing these tests, however, involved giving 1.75 Gm of glucose per kilogram of body weight in a fairly concentrated solution, and the possibility of the decrease being due to a change in blood volume must be borne in mind.

⁶ Broun, G. O., Ames, O., Warren, S., and Peabody, F. W. *J. Clin. Investigation* **1**: 295, 1925.

⁷ Whipple. Harvey Lecture, 1921-1922, vol. 95.

CLINICAL APPLICATIONS

The quantitative determinations of blood bilirubin, together with the type of reaction given, are of considerable importance in a variety of conditions, from the point of view of diagnosis and prognosis and as an index to the progress of the disease. This is true in cases of damage of various types to the liver, diseases of the gallbladder and biliary tract, diseases of the blood and blood-forming organs, and possibly other conditions in which the significance of the bilirubin is not as yet appreciated. At the same time, a quantitative estimation of urobilinogen in the urine⁸ affords a valuable check and confirmatory evidence.

Probably the most important practical application of the determination is, as a routine measure, in patients receiving arsenicals, particularly of the arsphenamine group. Here it affords the earliest possible indication of damage to the liver. If a record of the blood bilirubin value is made at the commencement of the treatment and repeated at regular intervals during the course, one may proceed with safety as long as the reading remains normal. A rise of even a few milligrams is significant, and the patient should be treated accordingly. Any considerable rise calls for the immediate cessation of treatment. Once an arsenical hepatitis is established, determinations of the bilirubin afford a reliable evidence concerning the severity and progress of the lesion. The type of reaction given in these cases is always biphasic, though this is recognized with difficulty if the value is low. The tables illustrate results obtained by this method in various types of cases.

As will be noted from table 1, the bilirubin test in arsenical jaundice gives high results, despite the fact that the disease was marked in only one of the foregoing cases. Incidentally, the highest values that I have seen occurred in two cases of Weil's disease in Toronto General Hospital which are not included in the present series, at the height of the disease the readings were 340 and 370 mg., respectively, estimated according to the method described herein. This is considerably higher than occurs in presumably complete obstruction of the biliary tract.

In the two cases of arsenical dermatitis included in the series, the bilirubin content was not increased.

The patient in case 7 was a woman who two days after delivery showed a slight degree of jaundice without fever and with mild anemia, the jaundice progressed for six or seven days, and then gradually disappeared. In view of the biphasic reaction, a diagnosis of toxic hepatitis was made. The patient in case 8 was a woman with a 4 plus Wassermann reaction, who two years previous to the present admission

8 Wallace, G. B., and Diamond, J. S. Significance of Urobilinogen in Urine as Test for Liver Function, with Description of Simple Quantitative Method for Its Estimation. *Arch. Int. Med.* **35**: 698 (June) 1925.

had undergone a splenectomy for splenomegaly and severe secondary anemia. She now showed jaundice, enlarged liver and marked anemia. Syphilis may or may not have been the etiologic factor in the condition, which in many respects resembled Banti's disease.

As will be seen, the observations in cirrhosis are variable, depending largely on the type. As a rule, the portal variety shows the direct reaction of obstructive jaundice.

THYROTOXICOSIS

Eight patients with thyrotoxicosis were chosen at random from those under treatment in the wards, all showed typical signs and symptoms of hyperthyroidism with basal rates of from plus 35 to 75. The bilirubin was not over 2 mg per thousand cubic centimeters in any case,

TABLE 1—*Results of Tests for Blood Bilirubin in Conditions Involving the Liver*

Case	Diagnosis	Mg per 1,000 Cc	Reaction
1	Arsenical jaundice	15.6	Biphasic
2	Arsenical jaundice	83	Biphasic*
		72	Biphasic
		68	Biphasic
3	Arsenical jaundice	36	Biphasic
4	Arsenical jaundice	29.5	Biphasic
5	Arsenical dermatitis	2.5	Indirect
6	Arsenical dermatitis	1.5	Indirect
7	Hepatitis, postpartum	26.5	Biphasic
		18.5	Biphasic
8	Hepatitis, syphilitic	25	Biphasic
		42	Biphasic
		36	Biphasic
9	Hepatitis, syphilis, anemia	4	Indirect
10	Portal cirrhosis	34	Direct
11	Portal cirrhosis	24	Direct
12	Cirrhosis, ascites	1.5	Indirect
13	Cirrhosis, ascites	1	Indirect
14	Cirrhosis, ascites	1.5	Indirect

* Under thiosulphate treatment.

and it was as low as 0.5 mg. The consistently normal values would seem to indicate that the degree of possible damage to the liver, so far as these cases were concerned, is so slight as not to effect the bilirubin values to any discernible extent.

CONDITIONS INVOLVING GALLBLADDER AND BILE DUCTS

The results in cases of cholecystitis and cholelithiasis without obstruction show that the hepatitis that has been stated by various authors frequently to accompany these conditions is not as a rule demonstrable by increase in bilirubin content. In twenty cases of cholecystitis of varying grades of severity—several acute cases but none showing evidence of biliary obstruction—only one gave a reading over 3 mg (4 mg). Practically all readings taken individually would be concluded to be normal, and determinations of bilirubin in this condition would appear to have little diagnostic value, particularly in the chronic

stage It is interesting to note, however, that if the average reading for the group is taken, 1.85 mg, it is approximately 50 per cent higher than that shown by the group of normal persons That this may be of significance in indicating a slight degree of hepatitis is possible

Two patients with catarrhal jaundice were seen in this series, giving readings varying from 30 mg to 15.5 mg In one case the patient gave a direct reaction at the height of the condition, all other reactions were biphasic

In cases of common duct stone and occlusion of the common duct by tumors, the bilirubin tests gave varying values, the highest being 142 mg in a case of carcinoma of the pancreas The principal value of the determination is in following the degree of the obstruction

TABLE 2—Results of Tests for Blood Bilirubin in Conditions Involving Blood *

Case	Diagnosis	Mg per 1,000 Cc	Reaction
1	Pernicious anemia	19.5	Indirect
2	Pernicious anemia	19.5	Indirect
3	Pernicious anemia	18.5	Indirect
4	Pernicious anemia	16.5	Indirect
5	Pernicious anemia	15	Indirect
6	Pernicious anemia	14	Indirect
7	Pernicious anemia	14	Indirect
8	Pernicious anemia	11	Indirect
9	Pernicious anemia	9	Indirect
10	Pernicious anemia	8	Indirect
11	Pernicious anemia	7	Indirect
12	Pernicious anemia	5	Indirect
13	Pernicious anemia	4.5	Indirect
14	Secondary anemia	3.5	Indirect
15	Secondary anemia	2.5	Indirect
16	Secondary anemia	2	Indirect
17	Secondary anemia	1	Indirect
18	Secondary anemia	1	Indirect
19	Sprue with anemia	3	Indirect
20	Hemolytic jaundice	3.5	Indirect
21	Splenic anemia	5	Indirect
22	Splenic anemia	7	Indirect
23	Hemolytic anemia, pregnancy	14.5	Indirect
24	Purpura hemorrhagica	2	Indirect
25	Paroxysmal hemoglobinuria	2	Indirect

* These represent maximum values obtained in each case

In table 2 are given the maximum values obtained in the individual cases seen in the wards over a period of some months Many of these cases gave considerably lower readings on various occasions, indicating the value of repeated determinations It has been pointed out by many observers⁹ that the blood in pernicious anemia has an increased bilirubin content, although not to the extent shown in the foregoing series This increase can often be surmised from the appearance of the serum alone, deceptive as this frequently is It will be noted that as a rule the variation in values between primary and secondary cases of anemias is distinctly marked The borderline case with values of from 3 to 5 mg per hundred cubic centimeters presents the greatest difficulty A case of primary anemia undergoing a remission will give values as low as

lower than this. Here repeated estimations over a period of time are necessary, and too much reliance must not be placed on the bilirubin value as a means of diagnosis. Any reading over 3 mg, however, should render one suspicious of a hemolytic factor.

Determinations at regular intervals also constitute a valuable means of determining the progress of a case, effect of treatment and other factors. The occurrence of a remission will be indicated by a decrease in bilirubin some days before any definite change will occur in the blood count other than an increase in the reticulated cells. The course of a typical case (case 4) is shown in table 3.

Case 23 in table 2 represents an interesting case of anemia in pregnancy. On admission, at the stage of seven months, the patient showed

TABLE 3—*Variations in Bilirubin in Case 4*

Date	Hemo- globin	Red Blood Cells	Mg per 1,000 Cc	Remarks
11/30/26	30	1,110,000	15.6	Feeding with spleen commenced
12/ 3/26	25	1,120,000	16.5	
12/ 8/26	25	1,100,000	15.5	
12/14/26	25		15	Regular high liver diet instituted
12/17/26				
12/21/26	25	980,000	14.5	
12/23/26	30	1,310,000	10.5	
12/28/26	31	1,810,000	7.5	
1/ 4/27	40	1,990,000	5.5	
1/10/27	18	2,490,000	2.5	

TABLE 4—*Results of Tests for Blood Bilirubin in Lead Poisoning*

Case	Mg per 1,000 Cc	Remarks
1	1.5	Mild symptoms, trace of lead in urine
2	2	Mild symptoms, history of exposure, no lead in urine
3	4.5	Moderate symptoms, lead in urine
4	5	Moderate symptoms, lead in urine

a severe anemia, primary in type, and required several transfusions before term. The bilirubin value, which had persistently been about from 12 to 14 mg per thousand cubic centimeters, fell to 7 mg within four days of delivery and thence to normal.

Case 25 was one of paroxysmal hemoglobinuria in which an effort was made to demonstrate an effect on the blood bilirubin of exposure to cold by testing blood before and one hour after immersion in cold water. No perceptible change was noted, neither, however, was hemoglobinuria produced.

The occurrence of jaundice of various grades in lead poisoning has long been a subject of speculation. In 1839, Tanquerel reported fifty-one cases of clinical jaundice in 1,217 cases of lead colic. This jaundice has been variously ascribed to direct hemolytic action of lead on the red cells and also to lesions in the bone marrow. Heubel, in 1871, obtained evidence of hemolysis in these cases by finding increased pig-

ment in the serum, bile and urine. The direct action on the red cells has been more recently demonstrated by Aub, Fairhall and others¹⁰. It is most probable that this is the cause of the constant mild secondary anemia in lead poisoning. The small series in table 4 would appear to indicate the possibility of determinations of bilirubin being of some value in the diagnosis of this condition. Further studies in this connection on a larger series would be of interest.

SUMMARY

A study was made of the blood bilirubin values in the normal person and in a series of cases representing various conditions in which abnormality in this regard might be expected. The technic used was that of Thannhauser and Andersen, with some slight modifications which I believe offer greater convenience and accuracy.

The normal range was from 0.5 to 3.5 mg per thousand cubic centimeters of blood. The effect of race and sex was not apparent, and that of pigmentation was slight. Fasting specimens gave slightly lower results.

I believe the determination to be of considerable value in patients receiving arsenical preparations as giving the earliest possible indication of damage to the liver. In cases of disease of the liver, important information is often given, but the type of reaction must not be entirely relied on as a means of diagnosis. Characteristically, there is no discernible effect in cases of cholecystitis and cholelithiasis without obstruction, twenty cases giving results which were within normal range, with one exception. The bilirubin is a valuable adjunct to the diagnosis and prognosis in diseases of the blood and blood-forming organs.

That the estimation may be of value in other conditions I believe possible, and in this class I would include lead poisoning, where the results warrant further investigation.

10 Aub, Fairhall, Minot, Reznikoff. Medical Monographs no. 7.

PERNICIOUS ANEMIA AND TROPICAL SPRUE

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Because of some recent papers suggesting, and in some cases even stating, that tropical sprue and pernicious anemia are the same disease, it has seemed worth while to give some of our observations on cases of sprue, especially comparing those that are typical of the latter condition. The identity of these two diseases has been particularly insisted on by Wood,¹ who has accepted Ashford's theory that *Monilia* causes sprue, and who has been able to take cultures of this yeast in all of his recent cases of pernicious anemia. He quite rightly says that for those who believe *Monilia psilosis* is the cause of sprue, the finding of this organism in pernicious anemia is one more point tending to prove the identity of these two diseases. We have recently published our results² with mouth and stool cultures in eleven cases of sprue and seventeen cases of pernicious anemia. Recently also Reed and Wyckoff³ have written on the similar changes found in sprue, pernicious anemia and combined degeneration of the spinal cord. They have not been able to grow *Monilia* in their cases of sprue, they have found the blood picture of pernicious anemia and evidences of degenerative changes in the spinal cord. In a paper on the achlorhydria family tree of diseases, Christian⁴ gives the similar observations in sprue and pernicious anemia, he suggests that these diseases may be the same and also that sprue may develop into pernicious anemia. Bramwell⁵ has listed the similarities in the physical observations and blood picture, but admits that there is not the emaciation in pernicious anemia that there is in sprue. Priston⁶ has written on the similarity of the appearance of the tongue in the two conditions. Van der Scheer⁷ stated that the presence of hydrochloric acid in sprue would differentiate the two diseases.

1 Wood, E J. Pernicious Anemia in Its Relationship to Sprue, Am J Med Sc **159** 28, 1925

2 Baumgartner, E A, and Smith, Glenn, D. *Monilia Psilosis* as a Cause of Tropical Sprue, Am J Trop Med **6** 433 (Nov) 1926

3 Reed, Alfred C, and Wyckoff, H A. The Common Picture of Sprue, Pernicious Anemia, and Combined Degeneration, Am J Trop Med **6** 221, 1926

4 Christian, H A. The Achlorhydria Family Tree of Diseases, Northwest Med **24** 531, 1925

5 Bramwell, Sir B. Sprue and Pernicious Anemia, Brit M J **1** 365, 1924

6 Priston, J L. The Tongue in Addison's Anemia, Brit M J **1** 216, 1924

7 Van der Scheer, A. Sprue and Pernicious Anemia, Nederl Tijdschr v Geneesk **2** 1468, 1924, abstr, J A M A **83** 1548 (Nov 8) 1924

Hampson and Shackle,⁸ under a title of megalocytic and nonmegalocytic anemias, have found that in these two diseases, as well as in bothrioccephalus anemia, the red cells are much larger than in many other diseases. Elders⁹ also has written concerning the similarity of the anemia in the two conditions.

DIAGNOSIS

Although pernicious anemia has been studied and written about a great deal, there is probably some difference in opinion as to what is requisite for a diagnosis. Hurst¹⁰ has recently taken up this subject, especially the emphasis to be placed on the presence or absence of hydrochloric acid in the gastric contents in this disease. From a series of cases of pernicious anemia from the literature and from his own experience he finds that in 98.3 per cent of the cases there is achylia, although he concludes that the diagnosis of pernicious anemia is not justified when hydrochloric acid is present. Levine, as well as several other writers, has found hydrochloric acid in several of his cases of pernicious anemia. If such cases can be accepted as pernicious anemia, then at least one if not two of the cases recently discussed as atypical anemia by Munford¹¹ should be diagnosed as pernicious anemia. So far our clinic has not been ready to accept that diagnosis in cases in which hydrochloric acid was found.

The question of anemia, of course, arises more often than any other and although the blood picture of pernicious anemia is well known, it may be well to list again the points that are generally accepted. There is a low red cell count, often below 3,000,000, and a relatively high hemoglobin content, giving a color index over 1. Poikilocytosis, a marked variation in the size of red cells and especially the occurrence of large red cells, polychromatophilia, stippling and megaloblasts or large nucleated red cells are found on examining the blood smear, a low white cell count, a high lymphocyte percentage and a low platelet count complete the usual picture. Recently again an article has appeared by Faber and Gram¹² suggesting that they do not consider a high color index so essential to a diagnosis of pernicious anemia as do some others.

Another difficulty in comparing the two diseases is that the cause of pernicious anemia is not yet known, and many have not accepted

8 Hampson, A. C., and Shackle, J. W. Megalocytic and Nonmegalocytic Anemia, *Guy's Hosp. Rep.* **74** 193, 1924.

9 Elders, C. Tropical Sprue and Pernicious Anemia, Etiology and Treatment, *Lancet* **1** 75 (Jan. 10) 1925.

10 Hurst, Arthur F. The Pathogenesis of Subacute Combined Degeneration of the Spinal Cord with Special Reference to Its Connection with Addison's (Pernicious) Anemia, Achlorhydria and Intestinal Infection, *Brain* **48** 218, 1925.

11 Munford, S. A. Atypical Anemias, *Clifton M. Bull.* **11** 139, 1925.

12 Faber, K., and Gram, H. C. Relations Between Gastric Achylia and Simple and Pernicious Anemia, *Guy's Hosp. Rep.* **74** 193, 1924.

Ashford's views that *Monilia psilosis* is the cause of sprue. Smith¹³ has recently given some experimental proof of the latter view. Wood's¹ finding of *Monilia* in his cases of pernicious anemia has been noted. In our first report of bacteriologic observations on eleven cases of sprue and seventeen cases of pernicious anemia we showed that this organism was often present. It was also found in five of eighteen other cases with diarrhea.

The pathology of pernicious anemia is better known than is the cause. It has long been known that irregular small ulcerations occur in the mouth in sprue. These appear to be acute ulcers, from which some experimenters have grown *Monilia*. Ulcerations in the lower part of the digestive tract have been described, but less is known about them. The thinning of the wall of the digestive tube has been mentioned again and again, but we have found few autopsy reports to confirm this.

As Wood has stated the distinguishing characteristics of sprue and pernicious anemia are not always well marked. Ordinarily in cases of pernicious anemia there is a fairly typical history of loss of appetite, sore tongue, no special loss of weight and certain neurologic symptoms. Clinically, a smooth or inflamed tongue, a lemon-tinted skin in a fairly well nourished patient and various neurologic observations of combined degeneration of the spinal cord are found. The changes in the spinal cord have been said to occur in about 80 per cent of the cases (Waltman, 1924). With achylia and a more or less characteristic blood picture the diagnosis of pernicious anemia is justified.

In a pronounced case of sprue the patient will usually have diarrhea or the history of diarrhea with large frothy stools, ulcers of the mouth, marked loss of weight, and weakness and neurologic symptoms like those in pernicious anemia and sometimes like those in tetany, which is said to occur later in about one fourth of the cases. These patients are emaciated, have ulcers of the mouth, a distended abdomen and, occasionally, evidence of tetany. There may be an Addisonian-like anemia and achylia.

DISCUSSION OF CASES

We have therefore again studied the records of our cases of sprue with the idea of comparing them with the observations in cases of pernicious anemia, more particularly those made in a recent series of fifteen cases the records of which are more complete than those of the earlier cases. Some of these patients have been observed over a period of several months, some of them for two years. The records have been studied closely for the blood pictures and results of gastric examinations, as we possibly rely more on these two tests than on any other for laboratory aid in the diagnosing of pernicious anemia.

¹³ Smith, I. W. *Monilia Psilosis* Ashford in Severe Anemia Associated with Sprue Syndrome. *Philippine J. Sc.* **24** 147, 1924.

The changes found in the blood in pernicious anemia have been stated in the foregoing. Nine of the fifteen cases of sprue (table) had a color index over 1, but five of these showed an index less than 1 before the patients left our hospital. The highest color index was 1.4, and this patient showed a color index of 0.7 when discharged. Four of the patients had a count below 2,000,000 red cells and nine below 3,000,000. In the table, in the column for erythrocytes (column 2), in which two figures are given, they represent the lowest and highest figures obtained for that patient. As a rule, the lowest figure is the one found on entry, while the highest is the one obtained before the patient left. In the column for color index two figures for each case are shown only in patients in whom there was either a change in the color index or a marked change in the red cell count. The second figure of the two represents that obtained at the latest count. During observation here, seven of the patients had nucleated red cells, but megaloblasts were found only in the patient that died. Changes in the red cells were found in eleven cases and were marked in four (indicated by ++ in the table). Anisocytosis appears to be less marked but actual measurement of the cells in two cases (cases 4 and 6) showed the curve (Hampson and Shackle) of the cell diameters to be to the right of that found for normal cells. Eight of the cases showed a low number of leukocytes at some time, but in only four cases was the number of leukocytes low in the majority of the counts, while in three of these four cases and in five others there were over 40 per cent of lymphocytes in a majority of the counts. In nine cases the platelets were counted, in six, they were less than 100,000, which is definitely lower than normal.

Three of the fifteen patients with sprue did not show free hydrochloric acid in gastric fractional tests (cases 3, 8 and 9). On a fourth patient we did not make a test, but free acid was not present in the contents of the stomach at postmortem examination (case 1). Four months previously, an Ewald test at another clinic had showed a free acidity of 19 and a total acidity of 28 per cent in this case. In a fifth case (case 6) the patient refused any gastric examination, so our only method of testing for acidity was by means of the alkaline tide, which was negative. Hubbard¹⁴ has shown that this test confirms either the presence or the absence of acidity in about 80 per cent of his cases, and we, therefore, accept this patient as being achylic. In this series of cases of sprue, then, there are five (33 per cent) with achylia which could be diagnosed pernicious anemia as far as this observation is concerned.

Other laboratory tests which may indicate pernicious anemia are tests for bile pigments, urobilin and urobilinogen of the urine or feces

14 Hubbard, R. S., and Munford, S. A. Alkaline Tide in Achlorhydria, *Arch Int Med* **35** 576 (May) 1925

Such tests were not performed on the feces, but in eight cases twenty-four hour specimens of urine were examined. Only three of these showed a definite increase in these compounds.

A recently described laboratory observation in some cases of sprue is a low blood calcium. This, as several investigators have shown, is often associated with a clinically demonstrable tetany. In four of the cases of sprue the calcium content was 7.3 mg per hundred cubic centimeters of blood or less, which is well below normal, in four others the blood calcium was from 8.3 to 8.6, which most investigators will agree is below the accepted normal. The blood fat was low in three cases tested and the blood cholesterol in two.

In the fifteen cases of sprue studied there has been a history of ulcers of the mouth. Besides this, two patients have complained frequently of a dry mouth. This caused a great deal of discomfort to one patient, and there was a history of ulcers early in the course of the disease which was all but forgotten. Six of the patients had ulcers in the mouth or on the lip during observation here, but three complained of a burning tongue when nothing unusual could be seen. In nine cases the tongue was definitely normal, while in cases 1, 4, 8 and 9, it somewhat resembled the tongue in pernicious anemia. The table also shows that there was loss of weight in all cases, and in seven this amounted to between one half and one fourth of the average weight.

Definite reactions showing tetany have been observed in only three cases. One of these (case 4) patients showed the tetany spasm on entry, in this case and in two others (cases 6 and 8) there were positive Trousseau and Chvostek signs. Of four patients tested with the electric battery, only one (case 4) gave the positive reactions of tetany, although one other gave suggestive reactions.

The reports on stool and mouth cultures in eleven of the cases of sprue and other conditions have been published elsewhere. In the last column in the table it can be seen that stool cultures were positive in all cases of sprue except in case 14. In case 6 the first culture produced atypical *Mompha* which did not produce gas in maltose. Several cultures were made from the stools of case 13 before *Mompha* was obtained.

There have been listed also fifteen cases of pernicious anemia in which the various observations were compared with those in sprue. In only eight of our cases of pernicious anemia have tests been performed to determine the blood calcium. In one case the blood calcium was 8.6 mg per hundred cubic centimeters of blood, which was the only case in which this constituent was below normal. The remainder ranged in the normal limits from 9 to 11 mg per hundred cubic centimeters of blood. Stool culture showed that in five cases *Mompha* was grown, one of which was atypical in its reactions on the sugars. In one case *Mompha* was grown from the gastric contents obtained for fractional analysis.

Laboratory Observations in Cases of Spue and Pernicious Anemia

Case	Red Blood Cells (in Millions)	Color Index	Red Cell Changes	Platelets	Gastric Acidity (autopsy)	A Cases of Sprue			Loss in Weight Severe 155 to 80	Neurologic Observations	Blood Calcium	Monilia Culture Tongue + Stools +
						Possible Pernicious Anemia	Lleetric	Tetany { Chvostek Trousseau				
						Yes				Negative	5 6	
1	2— 2—	1+	++	23,000	None (autopsy)				155 to 80	Negative	5 6	
2	4±	1—	None		Low normal			Negative	115 to 98	Negative	8 6	Stools +
3	2— 3 5+	1+ 1—	++ 0	98,000	None	Yes	Negative		Severe 150 to 98	Negative	8 3	Stools +
4	2 3 5+	1+ 1—	+ 0	68,000	Normal		Positive	Positive	Severe 110 to 67	Negative	6 2	Stools +
5	4±	1—	±	152,000	Normal				170 to 133	Negative	8 1	Stools +
6	2±	1+	+	34,000	Negative tide	Yes	Positive	Positive	160 to 101	Negative	7 3	Stools +
7	3— 4+	1+ 1—	±	285,000	Normal				121 to 90	Negative	11	Stools +
8	2— 3+	1+ 1—	++ +	107,000 74,000	None	Yes	Positive	Positive	130 to 108	Negative	3 1	Stools +
9	2 3±	1+ 1+	++		None	Yes	Negative	Negative	160 to 127	Not done	10 3	Stools +
10	1+	1—	None	239,000	Normal		Negative	Negative	170 to 117	Negative	8 6	Stools +
11	3±	1+ 1—	+	60,000	Normal		Negative	Negative	180 to 132	Not done	10 1	Stools +
12	4+	1—	None		Normal		Negative	Negative	125 to 99	Negative	9 0	Stools ±
13	2 4 6	1+ 1+	+		High normal				150 to 99	Negative	9 6	Stools +
14	1+	1—	None		Normal				200 to 160	Negative	11 3	Stools —
15	1 5	1—	None		High normal				160 to 117	Not done		Stools +

B Cases of Pernicious Anemia

				Negative	Yes				
1	2+	1+	++					Positive	Stools +
2	2 ₃	1+	++	None	Yes		130 to 104	Positive	Stools —
3	2+	1+	++	None	Yes		150 to 114	Positive	Stools + Mouth —
4	2 ₄	1+	++	None	Yes or subacute combined degeneration Proved autopsy		140 to 120	Marked	Tongue —
5	3 ₄	1+	+	None			127 to 117	Positive	Stools — Mouth —
6	3—	1+	+	None	Possible cancer (autopsy elsewhere) Yes		75 pounds loss	Positive	Stools +
7	3+	1+	+	None				Positive	Mouth —
8	1+	1+	++	Ever old none	Yes		150 to 135	Positive	Stools +
9	2— 3	1— 1+	++	None	Yes		147 to 135	Negative	10 7
10	2+	1+	++	None	Yes		130 to 120	Very slight	Stools
11	3—	1—	+	None	Yes		150 to 145	Positive	Gastric con- tents +
12	1+ 4	1+ 1—	++ +	None	Yes			Slight	Stools — Mouth —
13	3—	1+	++	None	Yes		None	Positive	Stools —
14	2+ 3	1+	++	None	Yes or subacute combined degeneration Yes			Marked	Stools —
15	3+ 3+	1— 1+	+	None				Marked	Stools + Mouth +

COMMENT

Several articles have appeared within the last few years in which various authors have tried to show that pernicious anemia and sprue are one and the same disease. Wood, in this country, has probably been the most insistent on this question. In sixteen cases of pernicious anemia he has been able to grow *Monilia psilosis* on cultures taken from either the mouth or the stools. We have taken cultures from the tongue or the mouth in seven cases of pernicious anemia, and so far have been successful in growing this organism in one (case 15). In our cases of sprue we took cultures from the sore tongue (case 1) or from definite ulcers (five cases), here also we failed, except in the first case, in which cultures were taken twice and were positive both times. Cultures from the stool in the cases of sprue were positive at the first attempt in thirteen of our cases, although one (case 6) did not yield an organism giving the accepted typical sugar reactions at the first culture. In one case (case 14) in which the patient had not had definite symptoms for eight years, only one culture was made, and typical *Monilia psilosis* was not found. In eight attempts in another case (case 12), *Monilia* was obtained only twice, one of which was atypical in maltose. In case 13 five cultures have been negative and only once was typical *Monilia* obtained. Our attempts at growing *Monilia* from the cases of pernicious anemia have been less successful, although this was not undertaken until we had had considerable experience. As is shown in another article, an organism giving the typical cultural reactions of *Monilia psilosis* was found in cultures from the feces in only three of seventeen cases, while in one, this organism was grown from the gastric contents. In the table we have added one more case (case 15) in which a positive culture was obtained.

If one would accept *Monilia* as the causative agent of sprue and, following Wood, also of pernicious anemia, then our results would at least indicate that the organism in the latter condition is less easily grown. Our technic and the mediums used for the two conditions were the same.

Many have called attention to the similarity of the anemia in the two diseases. Our figures show that as far as the color index is concerned, and this is the most frequently stressed point in the blood picture, it was over 1 in nine of our cases of sprue, but in five of these it became 1 — during the patient's stay in the hospital. So far, only one of our cases of pernicious anemia has shown this (case 11). Van der Scheer⁷ also found a high color index. Elders has given figures of blood counts in cases of sprue calling attention to a 1+ index. However, his quoted figures of erythrocytes and hemoglobin do not bear out his figures of color index, according to our method of calculating. Wood apparently has often found similar blood pictures in the two diseases.

In only one of our cases of sprue have we found megaloblasts. If one would lay stress on the blood picture, megaloblasts and large red cells are the most characteristic of pernicious anemia. The various changes in the red cells enumerated in the foregoing have certainly not been as marked in our cases of sprue as we would demand for criteria in diagnosing pernicious anemia. Various British investigators, especially Hampson and Shackle, have, following Jones'¹⁵ description, measured the red cells in various diseases, and have plotted curves of the number and the diameter of these cells. They found that in sprue, pernicious anemia and bothrioccephalus anemia the curves show that the red blood cells are larger than those in normal cases and in many other diseases. The red cells were measured in two cases of our series (cases 4 and 6). Both showed many large cells, the largest measuring well over 8 microns, thus confirming the resemblance between the red cells of sprue and those of pernicious anemia. Bastedo and Famulener¹⁶ found a high color index in two of their cases of sprue in which the patients died. In his cases of sprue Smith has described the typical blood count of pernicious anemia, but he has failed to find the cell changes characteristic of pernicious anemia. He mentions the lack of study of the bone marrow in sprue. In the case described by Baumgartner and Thomas¹⁷ (case 1), the bone marrow was certainly not typical of pernicious anemia, although the blood count and the postmortem achylia might suggest that diagnosis.

That there may be a profound anemia in sprue, no one doubts. Several of our patients have been severely anemic. That this helps to confuse the picture, we also admit. Wood's statement is also true, that the blood picture may be misleading, so that one disease may be mistaken for the other. Depending too largely on the presence of anemia and achylia, we, too, have wrongly diagnosed at least one case as pernicious anemia, one must not depend too much on the blood picture in diagnosing this condition. We believe that the anemia in sprue is as Smith¹³ found, aplastic. A high color index is not unusual in our series, but in most cases this became 1 — as the patient improved, a change also described by Elders. Recently Gram and Faber¹² have found this occasionally in pernicious anemia, but in our experience it is infrequent in the latter group.

If we accept achylia as a necessary observation in the diagnosis of pernicious anemia, then only five of our cases of sprue could be considered pernicious anemia (table). These five achylic cases had blood pictures that might readily be mistaken for the picture in pernicious

15 Price-Jones, C. Anisocytosis. Special Reference to Pernicious Anemia, Guy's Hosp. Rep. **74** 10, 1924.

16 Bastedo, W. A., and Famulener, L. W. Tropical Sprue, J. A. M. A. **81** 2102 (Dec. 22) 1923.

17 Baumgartner, E. A., and Thomas, W. S. A Case of Tropical Sprue with Autopsy, Chifton M. Bull. **11** 90, 1925.

anemia As a matter of fact, in three of our other cases of sprue there was almost as severe an anemia, but in these the presence of free hydrochloric acid would rule out pernicious anemia Priston⁶ stated that hyperacidity or normal acidity is found in sprue, unfortunately, this is not always true, at least it has not been true in our cases unless we have wrongly diagnosed the five achylic cases Bastedo and Famulener found that in most of their cases of sprue acidity was normal, although two patients that died were achlorhydric

Achylia is almost always found in pernicious anemia Faber and Gram believe that there was free hydrochloric acid in the stomach in five of their fifty-two patients with pernicious anemia Levine reported three such cases As stated, Huist found that in 98.3 per cent of the cases of pernicious anemia which he collected from the literature the patients had achylia

If the entire blood picture and the achylia are considered, it must be admitted that five of our cases might be called pernicious anemia We admit with Wood that any one without experience with sprue could readily fall into this error, even with some experience, we have done so in this clinic Such an error occurs when only these two observations are used in diagnosing these conditions

Although eight of our cases of sprue have had a low blood calcium, only four of these have been decidedly low, while in four it was no lower than in one of our cases of pernicious anemia As we did not know of any published figures giving the blood calcium in cases of pernicious anemia, we studied a few cases, and we found that this varied from 9 to 11.9, except in one case with a blood calcium of 8.7 which a week later was 10.4 Three of the five cases of sprue mentioned in the foregoing as possible cases of pernicious anemia had a low blood calcium, which, according to our figures, would be against the diagnosis of pernicious anemia

The loss of weight in sprue is often great In half of our cases the loss was from one fourth to one half of the patients' average weight The greatest loss noted was in three of the five cases that from the achylia and blood pictures could be called pernicious anemia We believe with Bramwell that usually there is not the marked emaciation in patients with pernicious anemia that one finds in patients with sprue, and the results in our table certainly do not show that there was a marked loss Probably all will agree that there is usually little loss of weight in patients with pernicious anemia, and yet this cannot be taken as an infallible observation, as we have recently found A markedly emaciated patient entered the clinic with a diagnosis of sprue A blood count and achlorhydria indicating pernicious anemia were found No neurologic symptoms and no changes in the spinal cord were found on physical examination, nor were there any signs of tetany What

was the diagnosis to be? The patient came from a region in which sprue is found, which further complicated the picture. The severe loss in weight we believed to be more characteristic of sprue. There was not the typical smooth tongue of pernicious anemia. The blood calcium was normal. Some blood serum was then tested by Macht, who has described a method demonstrating a toxic substance in the blood serum in cases of pernicious anemia¹⁸. This test showed a marked toxic substance in this patient.

Neurologic examinations have been made in almost all of our cases of sprue. Eight patients had the symptoms of numbness and tingling complained of in pernicious anemia. In one case (case 1) definite physical observations of degeneration of the posterior column was said to have been found at another clinic. In none of these cases have we found any definite changes indicating degeneration of the posterior column, and in the one case that came to autopsy (case 1) no changes in the spinal cord were found with the special stains used. But other nerve observations are sometimes present in sprue. Tetany was first described in this country in one of Bovaird's¹⁹ cases by Barach and Murray²⁰. We found evidences of tetany in three of our cases. So far as we know, this has not been described and is not present in pernicious anemia, yet two of these cases of tetany are among the five that may possibly be pernicious anemia, and in these two and in one other of the five there was a low blood calcium.

Mental depression is usually pronounced in sprue, and this has been rather infrequent in our patients with pernicious anemia. One of our cases of sprue (1913) was diagnosed neurasthenia for some months before the true condition was suspected. The numbness and tingling in the two diseases are almost similar, so that one wonders why degeneration of the posterior column, which occurs in pernicious anemia, is not found in sprue. Possibly when more necropsy material is available, such changes will be found. Parathyroid changes as evidenced by tetany were not found in case 1, although the patient had a blood calcium of 5.6 mg which at postmortem examination was found to be 5.3 per hundred cubic centimeters of blood.

Clinically patients with sprue have a different history from that of patients with pernicious anemia. The diarrhea in our cases of sprue was much more marked and constant than in our cases of pernicious anemia. Loss of strength and mental depression are more severe than we have noted in pernicious anemia. The type of diarrhea, loss of

18 Macht, D. I. A Study of the Toxin of Pernicious Anemia, *Proc Soc Exper Biol & Med* **23** 209, 1925.

19 Bovaird, D. A Study of Tropical Sprue or Psilosis, *J A M A* **77** 753 (Sept 3) 1921.

20 Murray, A. L., and Barach, A. L. Tetany in a Case of Sprue, *J A M A* **74** 786 (March 20) 1920.

weight and strength without a blood picture of pernicious anemia in one case made a differential diagnosis from pancreatic carcinoma difficult. The diarrhea in sprue often occurs in the early morning. The large, gray, frothy stools are characteristic, but may occur in pancreatic disease. One patient, case 3, returned in 1925 markedly underweight and severely anemic, but with fairly normal stools and without diarrhea, in case 7 the stools were not typical for a long time.

Clinical observations in the two conditions must be taken into consideration with the laboratory tests. As Wood has stated, the latter is too often stressed. We believe the severe loss in weight is characteristic of sprue, and we did not find this in our cases of pernicious anemia, except in the one referred to in the foregoing. A constant diarrhea, and especially the early morning diarrhea, is not often seen in pernicious anemia. The characteristic appearance of the tongue in cases of pernicious anemia has not been present in our cases of sprue. The small liver stressed by some as present in sprue was not especially notable in our series.

Differentiation of the two diseases is sometimes difficult. The unknown etiology of one and the not generally accepted theory of *Monilia psilosis* as a cause of the other gives little aid in distinguishing them. Wood's finding of *Monilia* in pernicious anemia confuses the picture still more. In our experience the almost constant finding of *Monilia* in sprue and inconstantly (20 per cent) in pernicious anemia and other conditions (25 per cent) lends some support to Ashford's views that *Monilia* is the cause of sprue, and fails to confirm Wood's contention that these two diseases are caused by the same organism. The presence of a toxic substance in the blood in pernicious anemia patients, as Macht has recently shown, may help to distinguish the two conditions or prove them identical diseases, and may also help in differentiation from the other confusing disease, subacute combined degeneration.

SUMMARY

We have discussed various observations, both laboratory and clinical, in patients with sprue or pernicious anemia. In fifteen cases of the former we found five with achlohydria and with an anemia similar to that of pernicious anemia—high color index—but possibly with less marked changes in the red cells, certainly fewer nucleated red cells. Three of the cases have had clinical evidences of tetany and a low blood calcium, an observation not yet described in pernicious anemia. None of the patients have had any evidence of degeneration of the posterior column while under our care, although several have had the marked numbness and tingling so frequent in pernicious anemia, while in fourteen of the fifteen *Monilia* has been grown from the stools, and this has occurred only four times in seventeen cases of pernicious anemia.

In a severely emaciated patient who had had marked numbness and tingling similar to that in pernicious anemia, as well as a similar blood picture, the spinal cord did not show combined degeneration and the bone marrow was definitely aplastic, yet the liver and kidney showed the iron pigment characteristic of pernicious anemia.

We do not feel that in our series the two conditions should be diagnosed as the same disease. We do not believe, as Christian suggests, that sprue is late pernicious anemia or the reverse, nor that even in late cases of sprue achylia necessarily develops.

In less than half of the cases of sprue in our series achlorhydria occurred. This is present in the more severe cases in which the anemia is more like that of Addison's type. Many of these patients lose a relatively large amount of weight, from one-fourth to one-half their average weight, some, probably all, experience severe numbness and tingling, and some have definite clinical tetany with a low blood calcium. Some cases probably cannot be correctly diagnosed, at least by methods now available.

HYPOGLYCEMIA AND THE TOXIC EFFECTS OF INSULIN ¹

GEORGE A. HARROP, Jr., M.D.

BAI FIMORI

Ever since the appearance of the first publication describing the group of symptoms accompanying overdosage with insulin, these symptoms have been generally considered to be associated with an abnormally low concentration of the blood sugar. A number of papers have subsequently appeared which report instances of spontaneous hypoglycemia accompanied by symptoms similar to those of insulin poisoning. These reports have served to strengthen the assumption that the hypoglycemia and the symptoms of insulin poisoning stand to each other in the relation of cause and effect. Hypoglycemia associated with pallor, muscular twitching, moist skin, irritability, collapse and stupor has been observed by Levine, Gordon and Derick ¹ in Marathon runners following severe exertion. Harris ² has reported hypoglycemia in two nondiabetic patients, associated with hunger, weakness and nervousness, which came on an hour before meals. The blood sugar value in these cases was from 60 to 70 mg per hundred cubic centimeters. If food was taken at intervals of not longer than from three to five hours, no such symptoms were observed. Hartman and Reiman (mentioned by Jonas ³) described a patient who experienced severe hunger three or four hours after meals, associated with unconsciousness. A subnormal blood sugar concentration was found, and the symptoms were relieved by food. Liu and Chang ⁴ have reported one of my cases, that of a man who experienced symptoms typical of mild overdosage with insulin during an attack of severe diarrhea associated with hypoglycemia. Holman ⁵ has reported similar phenomena following thyroid operations, although the clinical symptoms as described and their association with severe thyroid intoxication make the interpretation rather uncertain. John ⁶

¹ From the Medical Clinic of the Johns Hopkins Hospital and University.

1 Levine, S. A., Gordon, B., and Derick, C. L. Some Changes in the Chemical Constituents of the Blood Following a Marathon Race, *J. A. M. A.* **82** 1778 (May) 1924.

2 Harris, Seale. Hyperinsulinism and Dysinsulinism, *J. A. M. A.* **83** 729 (Sept 6) 1924.

3 Jonas, L. Hypoglycemia, *M. Clin. N. Amer.* **8** 949 (Nov.) 1924.

4 Liu, S. H., and Chang, H. C. Hypoglycemia. Report of a Case Unassociated with Insulin Administration, *Arch. Int. Med.* **36** 146 (July) 1925.

5 Holman, E. F. Hypoglycemia in Exophthalmic Goiter, *Bull. Johns Hopkins Hosp.* **34** 69 (Feb.) 1923.

6 John, H. J. The Lack of Uniformity in the Insulin Reaction, *Am. J. M. Sc.* **172** 96, 1926.

states that in eight normal persons during tests for glucose tolerance values between 31 and 57 mg per hundred cubic centimeters were found, always associated with extreme hunger. Josephs⁷ has reported toxic phenomena after fasting and during recurrent attacks of vomiting in children associated with low blood sugar values. In general, children appear to show hypoglycemia on fasting more frequently than do adults. Stenstrom⁸ has recently reported a case of spontaneous hypoglycemia in a lactating woman with tuberculosis and heart disease when fed on a diet of fat and vegetables. Symptoms of weakness, trembling and profuse sweating were observed, with hunger and a drawing feeling in the upper part of the abdomen, which were relieved when a normal diet was again given. The fasting blood sugar fell to 50, 40 and 50 mg per hundred cubic centimeters, respectively, on the three days during which symptoms were observed. As stated, this case bears a striking analogy to the observations of Widmark and Carlens⁹ on the puerperal paralysis of cows, which appears to be a hypoglycemic coma completely relieved by intravenous injection of dextrose.

An interesting association is with scleroderma, an example of which has been reported from this clinic by Dr Longcope¹⁰. A low fasting blood sugar content has been observed in other cases of scleroderma, together with hypotension, but neither is invariably present.

The association of severe diabetes with extreme emaciation, manition, diarrhea, hypoglycemia and coma without administration of insulin has been observed in this clinic, and similar cases have been reported from other clinics.

CASE 1—A man, aged 46, who had had diabetes for six years, with extreme loss of weight and emaciation, and more recently diarrhea and edema of the feet and ankles, had a blood sugar concentration of 54 mg per hundred cubic centimeters on admission to the hospital. There were no "hypoglycemic" symptoms. On unrestricted ward diet the blood sugar rose to 286 mg per hundred cubic centimeters, and sugar appeared in the urine. The diet was modified, and the fasting blood sugar fell to from 54 to 87 mg per hundred cubic centimeters. The basal metabolic rate was -20 . His condition seemed satisfactory until one morning five weeks after admission, when without warning he suddenly lapsed into a semistupor, and within half an hour was in deep coma, with slow respirations and somewhat increased pulse rate. The blood pressure was low—90 mm systolic and 70 mm diastolic. An examination of the blood sugar before death five hours later showed only 17 mg per hundred cubic centimeters. The intravenous administration of dextrose in this patient failed to elicit any response or the slightest improvement. He was under the care of Dr N. B. Herman, who will report the details more fully later.

7 Josephs, H. Fasting as a Cause of Convulsions, *Am J Dis Child* **31** 169 (Feb.) 1926, Recurrent Vomiting, *ibid* **31** 657 (May) 1926.

8 Stenstrom, T. "Spontane" hypoglykämische Reaktion bei stillender Frau, *Deutsches Arch f klin Med* **153** 181, 1926.

9 Widmark, E. M. P., and Carlens, O. Ueber die Blutkonzentration bei Kuhlen, *Biochem Ztschr* **156** 454, 1925.

10 Longcope, W. T. To be published.

It is possible that a part of the weakness and asthenia of Addison's disease, which, as is known, is usually associated with hypoglycemia and lowered blood pressure, may be due to a similar cause. Reports on studies of the effect of glucose in the treatment in this condition have not appeared. An interesting case report of an insulin-like reaction possibly produced by suprarenal insufficiency has recently been published by Stenstrom¹¹. Doubtless other conditions with coincident hypoglycemia unassociated with the administration of insulin will be reported in the future. One may conclude that a state of hypoglycemia may occur in a variety of conditions, accompanied by some or all of the following phenomena: Weakness, dizziness, pallor, sweating and hunger, mild disorientation, occasionally syncope and stupor and usually hypotension. Such hypoglycemia cannot be distinguished from that following overdosage with insulin.

On the other hand, hypoglycemia unassociated with any symptoms has been reported repeatedly. Jansen from Muller's clinic¹² in Munich has shown the frequency with which hypoglycemia occurs in the edema of undernutrition. He found a blood sugar concentration between 34 and 70 mg per hundred cubic centimeters in twelve of twenty-four cases, no acute symptoms occurred in any of these. The syndrome of edema, bradycardia, hypotension, polyuria, severe hunger and atrophy of the thyroid, lasting over a considerable period, bears no clearcut resemblance to reactions from insulin. Hypoglycemia has been reported several times in undernutrition, especially in children, but without symptoms. Gray has reported the results of examinations for blood sugar in 461 normal persons. Sixty-four of these had a fasting blood sugar concentration of less than 70 mg per hundred cubic centimeters, but they did not have any symptoms. It must be admitted that hypoglycemia of this grade has not often been seen in routine examinations of the blood sugar of fasting patients in this clinic.

For the proper adjustment of insulin dosage in cases of severe diabetes during the past two years, my co-workers and I have made blood sugar determinations on our patients at three or four hour intervals for a twenty-four hour period, in order to ascertain the proper balance between food distribution and insulin. Such determinations are readily made on capillary blood from the ear or finger either by the Hagadorn-Jansen method or by a microtechnic based on the Benedict-Folin-Wu method. We have been struck by the large number of low blood sugar readings, between 75 and 45 mg per hundred cubic centimeters, in patients with severe diabetes, both in those who have taken

11 Stenstrom, T. Einige Bemerkungen über spontanes hypoglykisches Coma, *Deutsches Arch f klin Med* **152** 173, 1926.

12 Jansen, W. H. Die Odemkrankheit, *Deutsches, Arch f klin Med* **131** 144, 1920.

insulin for a considerable period and in those who had received it for only a short time. Most of these patients have not had any symptoms of overdosage with insulin.

CASE 2—A man, aged 27, who had had diabetes for two years, and who had taken insulin for twenty months, was admitted to the Johns Hopkins Hospital with marked acidosis following a severe infection of the throat. He was finally rendered sugar-free on a rather restricted diet and the administration of 15 units of insulin three times a day before meals. An all day blood sugar curve was made, which showed a morning fasting blood sugar of 135 mg, a concentration of 130 mg at 11 30 a m just before lunch, 55 mg at 5 p m and 110 mg at 9 p m. Although there were no symptoms of a reaction in the late afternoon, it was deemed best to reduce the noon dose of insulin to 10 units. This was done, and two days later at 4 30 p m, he had definite symptoms of an insulin reaction, with weakness, pallor and sweating. The blood sugar concentration before the symptoms were relieved by orange juice was 60 mg per hundred cubic centimeters. It is impossible in such an instance as this to see any direct quantitative relation between the occurrence of the insulin reaction and the blood sugar concentration.

REACTIONS TO INSULIN IN PATIENTS WITH DIABETES MELLITUS

The present report is based on a study of patients with diabetes mellitus who have suffered insulin reactions while under treatment in this hospital during the past four years. Nearly all of the patients whose cases have been recorded in the past two years have been under my personal observation. It should be stated that most of the diabetic patients treated have had cases of great severity, and have been admitted either for regulation of insulin dosage or because of difficulties in management in the dispensary or because of other serious complications. For this reason large doses of insulin have been required in many cases and a much larger proportion of serious reactions has been observed than probably occur on the average among the whole group of patients who use insulin.

Toxic reactions to insulin may be conveniently divided into two groups. The first are the mild reactions, usually unassociated with conspicuous nervous or psychic manifestations. The second group comprises the more severe reactions, in which nervous or psychic symptoms largely or entirely dominate the picture. The frequent occurrence of this type of reactions has only recently received attention.

Mild Reactions—In the milder type of insulin reactions a group of symptoms occurs which is usually characterized by gradual development, and in which the subjective sensations described by the patients are often more pronounced than are the objective observations. The symptoms in this group in the order of their frequency are as follows: a sense of weakness usually generalized, less frequently referred to the abdomen, ordinarily appears first and is nearly always associated with a feeling of trembling or of actual tremor of the extremities. Combined with this may be a diminution of deep muscle

sense and sense of position, particularly in the legs. A sensation of coldness in the extremities, of numbness of the lips, hands or feet, of hunger, or less commonly of thirst are apt to appear. Tinnitus and diplopia occur in certain patients, the latter often in children. Actual sensations of acute pain have been absent, and the absence of actual premonitory aura such as occur in epilepsy is also noteworthy. The main objective physical observations are pallor and generalized sweating and occasionally a moderate rise in the systolic blood pressure, with a smaller diastolic increase. In mild reactions usually no change occurs either in the rate of the heart beat or of the respirations. Speech may be somewhat slurred and the mental response sluggish, but in most mild reactions there is really little change. The pupils tend to be dilated. It is usually assumed that if proper steps are not taken to end the attack promptly, unconsciousness, collapse or convulsions, may occur. This assumption has been given wide currency, probably by analogy to the results of experiments on animals. No deaths occurred in the present series as a direct result of overdosage with insulin. All of the phenomena described are not usually present in any one person. Of interest, however, is the tendency of the symptoms and the sequence of their development in a given patient to be repeated in later attacks. Flushing of the cheeks is much less common than pallor, but we have repeatedly seen mild reactions, characterized by conspicuous flushing of the face and neck.

Severe Reactions—Of more serious practical importance is the group of severe insulin reactions associated with nervous or psychic manifestations. Cases of this kind are less widely recognized, although good descriptions have recently appeared in the literature (Leyton,¹³ Severinghaus,¹⁴ Labbé¹⁵). At least two types are recognizable. The commonest type of such reactions among our cases is that associated with behavior more or less closely simulating alcoholic intoxication. Often there is a brief preliminary period in which the patient may appear dazed and tremulous, or in which he may at first have a sense of weakness and dizziness. Sweating is rather less common than in milder attacks. The patient may then become noisy, laughing or crying, there is incoordination of speech, the vision is obscured, and there is a characteristic loss of the inhibitions. The arms may be tossed about wildly, and there is a typical drunken, staggering gait, with resistance to attempts at restraint. Often delusions and ideas of persecution appear and the resemblance to the excitement stage of acute

13 Leyton, O. Hypoglycaemia, Proc Roy Soc Med **19** 37, 1926

14 Severinghaus, E. L. Hypoglycemic Coma Due to Insulin Overdosage, Am J M Sc **172** 573, 1926

15 Labbe, M. Les incidents des traitements prolonges per l'insuline, Bull et mem Soc med hôp de Paris **23** 1123 (June 25) 1926

alcoholism may be close. Obsessions and hallucinations may occur abruptly, or indeed without premonitory symptoms.

CASE 3—A man, aged 26, who had been suffering from severe diabetes for the last eighteen months, was admitted to the hospital in diabetic coma, from which he was restored by the usual measures. One evening a month later, when he was receiving 40 units of insulin a day, he suddenly became noisy and excited about an hour after supper. His face became pale, he tossed about the bed, talking in a loud voice and in a confused, irrational manner. He failed to recognize his wife and sister who were visiting him at the time. The blood pressure was unchanged, the blood sugar concentration was 65 mg per hundred cubic centimeters. The patient was quickly revived with orange juice, and later he had no recollection of the incident. This train of symptoms was repeated in an almost identical manner on two other occasions.

A characteristic feature of these attacks is the complete amnesia which the patient exhibits after recovery. His recollection is usually retained up to the moment when symptoms appear, and then it is lost completely.

CASE 4—A man, aged 57, with diabetes of five years' duration had been treated with insulin for the past eighteen months. One night he ate a light supper, having previously taken 12 units of insulin. Half an hour later he complained of cramplike pains in the legs and then vomited. He felt tired, went to bed and promptly fell asleep. At midnight he awoke and began talking loudly, tossing about in bed entirely disoriented, and resisting the attempts of his family to pacify him. His speech was thick and nearly unintelligible. He accused the medical attendant who was called to see him of wishing to do him bodily injury, and resisted all attempts at examination. At this time he was taking 12 units of insulin twice a day. He came out of this confusional state after he received orange juice and sugar, but he was not completely rational for an hour or more. He had no recollection later of what had happened.

Loss of Consciousness—A more serious type of disorder is that characterized by partial or complete loss of consciousness for longer or shorter periods. This often occurs without warning, or if any warning is given, it may be so brief that the patient does not have time to summon aid. It may occur during sleep, being recognized only in the morning when it is found that the patient cannot be aroused. The attack may be one of semistupor in which patients remain for varying periods, the longest which we have observed being sixty hours. When in this condition, the patient may lie totally unresponsive to any stimuli except pain. Resistance is usually offered, however, to manipulations, such as attempts at venipuncture or the insertion of an infusion needle. The patient is usually pale, and he often lies with the eyes half open, staring vacantly. When the eyes will follow light, coarse nystagmoid movements may be elicited. There is nothing characteristic of the behavior of the deep reflexes, which are usually unaltered. The temperature is frequently subnormal, the pulse and respirations are slowed, and the blood pressure is usually low. Irregularities of respiration have been seen in two of our patients, in one of

whom periodic breathing of the Cheyne-Stokes type was observed for a period of thirty minutes. While the patient is in coma, waxy flexibility of the extremities may be observed, and the whole picture much resembles that of catatonic stupor. When the reaction is prolonged, there may be periods of semiconsciousness with subsequent relapse into the state of stupor. The mental state during these periods of partial consciousness is somewhat difficult to define, but it is characteristic. The patient is dull and appears dazed, but may at times recognize persons and places. These occasional glimpses of rationality may deceive the observer into believing the patient's behavior a sham or into minimizing its seriousness.

From such severe psychic reactions or even actual unconsciousness patients may recover and become rational suddenly, or there may be a twilight interval lasting for several hours, which reminds one of the recovery from ether anesthesia or the sobering up after intoxication. A headache of varying severity is generally complained of after the attack, often lasting for several hours, and the patient is frequently drowsy and sleepy for some time. Mental depression following the attacks recalls strongly that which occurs after epileptic seizures. It is a common aftermath.

CASE 5—A woman, aged 24, a teacher, while attending a short course of instruction in a normal school near Baltimore was brought unconscious to the hospital with a history of having fallen over in a faint in the classroom about two hours previously. When seen she showed no evidence of trauma as a result of her fall. The temperature was subnormal, 97.8 F by rectum. The pupils were widely dilated, the neck was slightly stiff, the breathing slow and stertorous, the skin moist and the face and forehead perspiring freely. The limbs were equally flaccid, and the deep reflexes were absent or obtained with great difficulty. The heart and lungs were normal, and the blood pressure was 110 systolic and 60 diastolic. The urine was free from sugar, albumin and casts. The girl's previous medical history was not at once obtainable, as she had arrived in Baltimore two days previously. Poisoning was considered a possibility, and gastric lavage was performed, as a result of which only a large amount of undigested food was recovered. The complete and mystifying absence of any indication as to the cause of the continued unconsciousness after two hours' observation made a lumbar puncture appear necessary, when the girl suddenly awoke, sat up and asked for water. She then said that she had been under treatment for diabetes mellitus in a middle western city, had ceased visiting her physician about three weeks before, but had continued to take insulin. On the morning of admission, feeling hungry, she had taken a larger breakfast than usual and a double dose of insulin. She had felt rather faint in the class-room and then had known nothing more until she opened her eyes in the hospital. When her history was thus related, a belated specimen of blood was taken for an estimation of sugar, and the blood sugar value was reported as 65 mg per hundred cubic centimeters. For the rest of the day following her recovery she suffered from a severe occipital headache.

CASE 6—A woman, aged 20, who had been under treatment for diabetes of maximal severity in the clinic for upward of three years, and who took from 40 to 60 units of insulin a day, was brought into the hospital comatose at 2 a. m. Neighbors in an adjoining house had been awakened by screams and cries, had forced their way into her room, and had found her lying on the floor. A blood

sugar estimation showed that there were 50 mg per hundred cubic centimeters. She was at once given dextrose intravenously and by rectum, but notwithstanding the almost immediate return to a normal or even high blood sugar level, and the appearance of glycosuria, she did not recover consciousness. She cried at intervals during the following day, resisted violently all efforts at treatment or feeding, and was totally unresponsive to any questioning. Most of the time she lay with eyes half closed, staring at the ceiling as if in a dazed condition. Gastric lavage on admission was returned with a large amount of undigested food. As she had previously been despondent over her condition, the possibility of poisoning was also considered, but analysis of the gastric contents revealed nothing abnormal, and the results of examination of the blood for carbon monoxide were negative. On the second morning, about sixty hours after the beginning of the attack, she awoke, conscious and completely oriented, but with no recollection of the previous events. On the night previous to admission she had taken her usual evening dose of insulin at 9 o'clock when she ate her supper, and had gone to bed. About an hour later, she had awakened with a sense of oppression in the abdomen and a feeling of weakness and hunger. Recognizing the symptoms, she had tried to get out of bed for food, but had collapsed on the floor. She knew nothing more of what had occurred. During the entire time from admission to the hospital until the recovery of consciousness sixty hours later, sugar was constantly present in the urine, and the blood sugar ranged from 120 to 180 mg per hundred cubic centimeters.

CASE 7—A boy, aged 16, with diabetes of maximum severity, received four injections of insulin a day during a course of treatment in the hospital. 20 units before breakfast, 15 units before lunch, 20 units at 5 o'clock and 15 units at 10 p. m. This dosage and the distribution of the daily diet into four portions following each of the injections of insulin finally rendered the urine sugar-free, and estimations on the blood sugar before each of the meals were between 110 and 160 mg per hundred cubic centimeters. The patient felt well on this regimen, which was followed without incident for a period of a week. One night he complained of slight epigastric pain and had a loose bowel movement just before supper, but the insulin and supper were given as usual, as was the late evening dose and the late lunch following it. Next morning at 6 o'clock the nurse on making her morning rounds was unable to awaken the patient. On examination shortly after, he was found to have a subnormal temperature, and it was impossible to arouse him. There were slight twitchings of the face, and about the mouth, the extremities were relaxed and the deep reflexes were sluggish. The breathing was slow and deep, about 14 respirations a minute. The pulse rate was 56. The bladder was moderately distended. A blood sugar determination made at once showed 85 mg per hundred cubic centimeters, and a catheterized specimen of urine was free from sugar or acid bodies. As no other explanation seemed adequate to account for his condition, and notwithstanding the fact that the blood sugar was little below the normal fasting level, an intravenous injection of dextrose was given, whereupon the patient became conscious and normally oriented within ten or fifteen minutes. He was totally unaware of what had happened since receiving the injection of insulin and lunch about eight hours previously.

Wilder¹⁶ has recently stated that an increase in blood pressure occurs during insulin reactions as a constant and hitherto unmentioned phenomenon. In some of our cases a rise of from 20 to 30 mm in systolic pressure has occurred, with somewhat less increase in the diastolic pressure, so that the pulse pressure was increased. When the reaction is severe, however, or when complete or partial lack of con-

16 Wilder, Russell M. Hyperthyroidism, Myxedema and Diabetes, *Arch Int Med* 38 736 (Dec) 1926

sciousness supervenes, we have not found the pressure raised, and in the cases of actual coma it may be low. This is of some importance in differential diagnosis in cases in which patients are brought in unconscious, and in which in the absence of a history or of obvious marks of hypodermic injections, as has happened in three of our cases, the nature of the condition is doubtful. In these cases dilated pupils were present and the eyegrounds did not present abnormalities. The urine was free from albumin, and, as was to be expected, from sugar.

The diagnosis between a condition resulting from overdosage with insulin and diabetic coma does not usually present great difficulties even without laboratory aids. In the one condition, slow, shallow and at times irregular breathing occurs, in the other, hyperpnea, while the urinalysis quickly reveals the true state. Nevertheless, the tendency in some cases of diabetic coma toward a diminution of the urinary concentration and excretion of sugar is well known, and although none of the patients that we have observed have been free from glycosuria, such a condition has been reported in the literature. Patients in diabetic coma almost invariably show evidences of considerable or extreme dehydration, and such is not usually the case in coma due to insulin. The urine from our patients with severe insulin reactions has never shown the presence of acetone bodies. On the other hand, cases of diabetic coma have been reported in which acidosis has been due, at least in large part, to acids other than the acetone bodies. A determination of the blood sugar concentration and plasma bicarbonate will usually reveal the true condition and the presence or absence of acidosis.

Sevringhaus in reporting recently five cases with marked mental disturbance and unconsciousness lays stress on the production of these symptoms by repeated overdosage with insulin. Although severe reactions as a rule occur in patients with severe diabetes when large doses of insulin have been given over considerable periods of time, and while it would appear that, in general, emaciated persons are more prone to toxic reactions than are the well nourished, these generalizations are subject to exceptions. Insulin reactions of all types of severity may occur at any age, and mental disturbances in our series have not appeared more frequently in those who have previously had milder reactions.

It seems clear that the state of hypoglycemia alone is not always the cause or even the most important factor in the production of toxic symptoms. Patients in whom unconsciousness occurs may not revive for hours after the blood sugar has been elevated to normal or even higher by the administration of carbohydrate. On the other hand, recovery of complete consciousness may occur spontaneously even when the blood sugar is at a low level. Reactions of all shades of severity occur at various levels of the blood sugar. The series of cases recently reported by John⁶ is of interest in this regard. Of twenty-four cases

studied, a blood sugar concentration of 80 mg per hundred cubic centimeters or less occurred at the time of the reaction in only thirteen, while in the remaining eleven, it was above 80 mg per hundred cubic centimeters, and in five of these patients it was actually over 200 mg per hundred cubic centimeters when symptoms occurred. We have never seen such extreme cases of hyperglycemia in association with insulin reactions. We have, however, seen characteristic toxic insulin effects in four persons in whom the blood sugar taken at once and previous to the administration of carbohydrate was between 150 and 110 mg per hundred cubic centimeters. The following case is typical of this group.

CASE 8—A diabetic patient, aged 58, who had never received insulin, and whose fasting blood sugar was 340 mg per hundred cubic centimeters, was given an injection of 20 units of insulin during some metabolic studies. In the course of twenty minutes he became uneasy, faint and hungry, he sweated profusely, became pale and his blood pressure fell from 160 mm systolic and 95 mm diastolic to 130 mm systolic and 80 mm diastolic. A specimen of blood for the estimation of sugar was taken, and it was found to be 150 mg per hundred cubic centimeters. The urine was free from sugar and acetone bodies. As the patient's uneasiness grew much worse, the studies undertaken were discontinued, and the patient was given orange juice with cane sugar, which produced prompt abatement of all symptoms.

SUMMARY

The cases which have been studied indicate plainly the fact that unconsciousness due to insulin overdosage may supervene with great rapidity, often without warning in sleep, and with few or negligible prodromes. They also indicate that there is not always a set progression of symptoms such as is usually described. Not always do subjective symptoms of uneasiness or weakness or hunger precede more pronounced symptoms of pallor or flushing or sweating, in their turn preceding convulsions and unconsciousness. Generalized convulsions are exceptional in adults, although muscular twitchings, especially of the facial muscles and of the muscles of the extremities, are common. The clinical picture in two of our cases strongly suggested severe carbon monoxide poisoning, except that the coloring was not typical. The administration of carbohydrate to unconscious persons in insulin reactions does not always have the immediate prompt effect that we have been led to anticipate. It seems clear that the degree of hypoglycemia does not accurately determine the severity of the reaction, nor does the administration of sugar always relieve it. It is probable that the toxic effects may be due partly, or in certain cases entirely, to some other action of insulin. As Labbé has suggested, it is not possible to transfer directly to man the results of overdosage with insulin in animals. The psychic manifestations which are so common in man do not usually occur in animals, and in man there is wide individual variation in the response to overdosage.

THE SPECTROPHOTOMETRIC DETERMINATION OF HEMOGLOBIN ¹

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Within the last few years, a number of workers in the field of medicine have expressed dissatisfaction with the methods commonly used in determining the amount of hemoglobin in the blood. They have pointed out not only that the different types of hemoglobinometer use different values of concentration of hemoglobin for 100 per cent on the scale, but also that the methods themselves are for the most part not sufficiently accurate for use in diagnosis. Of these two objectionable features, the latter is, of course, by far the more serious. The confusion and misunderstanding caused by dissimilar scale values can be avoided simply by the adoption of a uniform method of reporting hemoglobin, as recommended recently by Lindsay, Rice and Selinger, ¹ but if the method itself is not sufficiently accurate, errors in diagnosis are unavoidable.

ACCURACY OF METHODS IN COMMON USE

In order to obtain some idea concerning the accuracy of the more commonly used methods for estimating hemoglobin values, it is pertinent to the subject under discussion to examine certain data which have recently appeared in medical journals.

In table 1 are shown the results of comparative readings made by various observers. All values have been reduced to the same scale for comparison, so that the various scale standards used in the different methods do not affect the results here shown. The readings obtained by Senty ² in his studies are indicated by points placed on several graphs exhibited in his paper. We have computed the average and maximal percentage differences from the values thus indicated by Senty. The same is true of the readings obtained by Brown and Roth,³ and we have computed the percentage differences shown in table 1.

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1 Lindsay, J W, Rice, E C, and Selinger, M A. A Plea for a Standardized Method of Estimating and Reporting Hemoglobin Values, *J Lab & Clin Med* **11** 737, 1926.

2 Senty, E G. A Comparative Study of Various Methods of Hemoglobin Determinations, *J Lab & Clin Med* **8** 591, 1922-1923.

3 Brown, G E, and Roth, G M. Prognostic Value of Anemia in Chronic Glomerular Nephritis, *J A M A* **81** 1948 (Dec 8) 1923.

It is evident from these results that the hemoglobin values given by the various methods differ greatly. When one considers that, with only two exceptions, no two methods here compared are found to agree on the average even to within 10 per cent, and that the maximal differences run from 26 to 56 per cent, one is convinced that altogether too much confidence is commonly placed in the readings given by the ordinary routine methods here represented.⁴ These data do not give conclusive evidence concerning the relative accuracy of the different methods, since only the last three sets of readings in the table are compared with a method of proved accuracy (the van Slyke). The following points are worth noting, however. Readings by the Newcomer method are found by Lindsay, Rice and Selinger to vary from the van Slyke readings by

TABLE 1—*Comparative Readings of Hemoglobin by Various Methods*

Observer	Method	Observations	Difference (per Cent) From Result by Method Indicated Below			
			Cohen and Smith		Newcomer	
			Average	Maximal	Average	Maximal
Senty	Dare	91	17.3	40	13.9	29
	Newcomer	91	6.0	40		
	Tallqvist	91	17.2	56	14.8	31
Brown and Roth	Dare		Haldane-Palmer			
		72 (0.70 per cent on Dare scale)	10.6	26		
		89 (above 70 per cent on Dare scale)	27.5	46		
Lindsay, Rice and Selinger	Dare		Van Slyke Oxygen Capacity			
		(3 instruments)	7 23.7	Not given by authors		
			3 27.3			
	Newcomer Sahli	7	2 38.0			
		7	2.1			
			36.9			

only 2.1 per cent. However, too few comparative readings (seventeen) were taken to warrant conclusions. Senty finds the Newcomer method to give readings differing on the average by only 6 per cent from the Cohen and Smith readings, yet many of the individual differences are great, varying from -24 per cent (not shown in table) to +40 per cent. Only 82 per cent of all the ninety-one readings are in agreement to within 10 per cent. Therefore, judging from these data, we must conclude that neither the Newcomer method nor the method of Cohen and Smith is shown to be highly reliable, although the evidence is somewhat favorable to them.

All the data concerning the Dare hemoglobinometer lead inevitably to the conclusion that the readings are unreliable, unless one is willing to

4 The van Slyke oxygen-capacity method is sufficiently accurate, but it is not ordinarily used as a routine procedure because of the labor and time involved.

attribute the lack of agreement to the other four methods with which the Dare is compared. The latter alternative is not reasonable, however, especially since one of the four methods, the van Slyke, is known to be accurate to within 1 or 2 per cent. Again, it is interesting to note that Senty finds the Dare readings to agree with the Cohen and Smith and with the Newcomer readings little better than do the readings by the Tallqvist method. Since the latter method is commonly, and correctly, regarded as unreliable, this comparison is further evidence of the inaccuracy of the Dare method.

As to the Sahli hemometer, the seven readings taken by Lindsay, Rice and Selinger indicate that the instrument is highly inaccurate. Possibly the average difference from the van Slyke readings would be lower if more readings were compared. It is clear, however, that no method can be considered reliable in diagnosis if seven values are found to show an average error of 36.9 per cent.

We are hardly justified in drawing conclusions as to the accuracy of the Haldane-Palmer method, since it is compared only with the Dare method, with which it is in poor agreement.

Observations on the data in table 1 may be summarized briefly in the following conclusions:

1. All the evidence here shown indicates that the Dare, the Sahli and the Tallqvist methods are entirely too unreliable for use in accurate diagnosis.

2. The evidence concerning the method of Newcomer and that of Cohen and Smith is partly favorable and partly unfavorable.

3. No reliable conclusion can be drawn from these data concerning the Haldane-Palmer method.

OBJECT OF THE INVESTIGATIONS

The object of the present work has been to investigate the possibilities of the spectrophotometric method of determination of hemoglobin (1) for the use in routine diagnosis, (2) for standardization purposes and (3) as a research method. Briefly stated, the investigations were prompted by (1) a growing dissatisfaction with the methods now in common use, because of their general unreliability, as illustrated in table 1, (2) the need for a standardizing method which is at once highly accurate, fairly simple, and capable of being reproduced at any time without uncertainty or ambiguity, and (3) the desirability for research workers to have at their disposal a method sufficiently simple and accurate to be used in following closely the course of treatment in its effect on hemoglobin concentration, or in investigating any question which may arise in regard to the value or variation of the concentration in states of health and disease.

THEORY AND EXPERIMENTAL METHOD

The theory of spectrophotometric determination of the amount of hemoglobin or other substance in solution is well known. When light is allowed to pass through a solution of a colored substance, such as hemoglobin, it is found in general that the different wave lengths are transmitted unequally. If one plots the fraction of light transmitted at each wave length, the spectral transmission curve for that particular substance is obtained. No two substances have spectral transmission curves of exactly the same shape, so in general one may with certainty identify a substance from the shape of its curve. The transmission of light of various wave lengths (from red to violet) by oxyhemoglobin (curve 1) and acid hematin (curve 2) are given in chart 1. For curve 1 the dilution was one part by volume of blood to 200 cc (approximately) of 0.1 per cent solution of sodium carbonate, in curve 2 the dilution was also 1:200.

Again, the fraction of light transmitted by the substance at any given wave length can be used in calculating the concentration of the substance in the solution, providing the value of a certain constant called the absorption ratio is known for that wave length. The value of this absorption ratio is given by the relation

$$A = CD' \quad (1)$$

in which A is the absorption ratio, C is the concentration of the substance and D' is the thickness of solution which transmits only one tenth of the amount of light (of that particular wave length) which enters it. From this relation, one has

$$C = \frac{A}{D'} \quad (2)$$

As a rule, however, it is not convenient to make the thickness of solution examined exactly equal to the length D' . If the thickness is some other length, D , then it may easily be shown that

$$D' = -\frac{D}{\log_{10} F} \quad (3)$$

in which F is the fraction of light transmitted by the thickness D . Substituting this value in equation (2), one has

$$C = -\frac{A}{D} \log_{10} F \quad (4)$$

Since A and D are constants, this equation simply means that the concentration of the hemoglobin or other substance in the solution is proportional to the negative logarithm of the fraction of light transmitted.

This gives a simple method for estimating the amount of hemoglobin in blood. The values of A and D being known, it is necessary only to measure the fraction of light transmitted and to substitute this number for F in equation (4), or, simpler still, it is possible to make use of a curve plotted from equation (4) to read the concentration of hemoglobin directly from the curve as soon as the value of F has been found. A curve of this type, used in our investigations, is shown in chart 2. If the answer is obtained from a curve in this manner, and if one uses a direct reading spectrophotometer in finding F , then no computation of any kind is required.

As a rule, the spectral transmission curve of a colored substance in solution shows one or more absorption bands. The number, position and intensity of these bands are characteristic of the absorbing substance, differing in general even for different derivatives of the same substance. In the present determinations of concentration of hemoglobin, the transmission in the region of maximal absorption in one of the absorption bands of oxyhemoglobin was measured. The band chosen was the so-called β -band situated in the greenish yellow region of the spectrum. In this band, maximal absorption takes place at a wave length of approximately 542 millimicrons. This was determined by a series of examinations

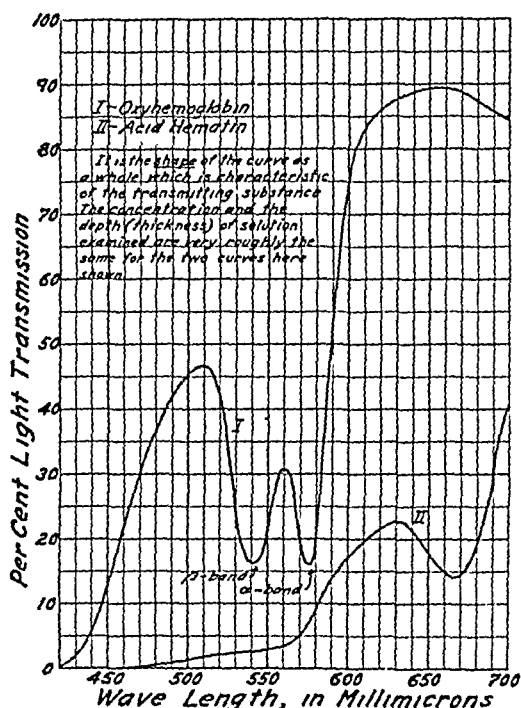


Chart 1—Characteristic spectral transmission curves of oxyhemoglobin and acid-hematin. I is the curve for oxyhemoglobin, II the curve for acid-hematin. It is the shape of the curve as a whole which is characteristic of the transmitting substance. The concentration and the depth (thickness) of solution examined are roughly the same for the two curves.

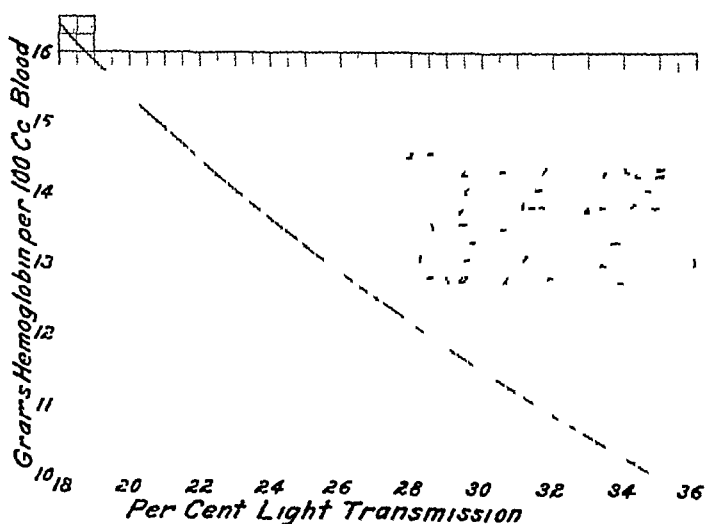


Chart 2—Curve from which the hemoglobin concentration was read off without computation. Experimental conditions were blood diluted to 1:200 with 0.1 per cent sodium carbonate solution, then thoroughly shaken with air to form oxyhemoglobin, thickness of solution, 1 cm, wave length of light, 542 millimicrons, value of absorption ratio, 0.001,100.

of the shape of the transmission curve in this region. Accordingly all measurements were made at a wave length of 542 millimicrons.

All transmission readings were taken on the direct reading spectrophotometer of recent design, manufactured by Keuffel and Esser, and called by them a "color analyzer." This instrument is more conveniently and rapidly operated than the usual type of spectrophotometer. To obtain light of any particular wave length, it is necessary only to turn a graduated dial to the proper setting. The light comes from two brightly illuminated blocks of magnesium carbonate situated at the rear of a lamp-house containing two 400 watt lamps, and passes through two parallel tubes with glass ends, one containing a solution of the substance to be examined, the other containing the solvent only. Equal illumination of the two halves of the optical field is obtained by rotating a graduated cylindric head by which the amount of light of any desired wave length passing through the standard solvent may be modified at will, and from which the percentage of transmission may be read off directly. Thus the fraction of light transmitted at any given wave length may be determined without computation of any kind.

The following technic was used in the determinations of hemoglobin concentration. The specimen of blood was obtained by venipuncture and at once shaken with about 20 mg of powdered potassium oxalate to prevent clotting. As a rule, about 20 cc of blood was drawn in order to insure a sufficient quantity for the various tests which it might be desirable to make. However, only a small amount was necessary for use in the hemoglobin determination. A small part (usually 0.05 cc) of the specimen of blood was diluted to 1/200 with 0.1 per cent sodium carbonate solution, by means of carefully calibrated pipets. It was then thoroughly shaken with air to change the hemoglobin to oxyhemoglobin, one of the two analyzer tubes of the spectrophotometer was filled with the solution, and the fraction of light transmitted at a wave length of 542 millimicrons was obtained by averaging several (usually ten) readings. Analyzer tubes of 1 cm in length were used. The fraction of light transmitted gave the value of the term F in equation (4), so that the hemoglobin concentration, C , could be calculated. Instead of substituting in equation (4), however, our results were read off directly from a curve (chart 2) obtained by plotting equation (4) as previously described.

The procedure therefore consists of the following steps: (1) dilution of the specimen of blood, (2) shaking with air, (3) filling the analyzer tube with standardized solution, (4) taking the transmission readings, and (5) reading the hemoglobin concentration from the curve. If the dilution is made with a diluting pipet similar to those used in blood counting, the entire procedure can be carried out in about five minutes. The method therefore is neither laborious nor time consuming. There are no corrections to be made. Computations of any kind are not necessary, since the result is obtained from a curve.

DETERMINATION OF THE ABSORPTION RATIO

In order to use equation (4) it was necessary to know the value of the absorption ratio A for oxyhemoglobin for the wave length employed, namely, 542 millimicrons. Williamson,⁵ in his studies on hemoglobin in 1916, found the average value of A for oxyhemoglobin for the spectral region between wave lengths 534 and 542 millimicrons to be about 0.00118 (the average of two determinations, 0.001168 and 0.001190). The value at wave length 542 millimicrons has never before been determined, however. In determining it the following method was employed.

Fifteen different specimens of blood, obtained by venipuncture and treated with a small amount of powdered potassium oxalate to prevent clotting, were tested for hemoglobin content by the van Slyke oxygen capacity method. For these tests we are indebted to Dr. E. J. Baldes, of the Section on Physics of the

5 Williamson, C. S. Influence of Age and Sex on Hemoglobin, *Arch. Int. Med.* **18**: 505 (Oct.) 1916.

Mayo Clinic The tests were carefully carried out, with the latest improved van Slyke apparatus In every case (except one) two or more independent determinations were made and the average taken as the correct value of the hemoglobin concentration for the specimen under test It is felt, therefore, that considerable confidence can be placed in the accuracy of the results All the specimens were tested for methemoglobin by a sensitive spectrometer, and it was not found in any Such tests were thought desirable since the presence of methemoglobin would affect the comparative values as determined by the oxygen capacity and spectrophotometric methods Part of each specimen of blood was also diluted to 1:200 with 0.1 per cent sodium carbonate solution, shaken thoroughly with air to secure oxygenation, and tested with the direct reading spectrophotometer for transmission at a wave length of 542 millimicrons, the procedure being exactly the same as that followed in obtaining the hemoglobin concentration by the spectrophotometric method In order to increase the accuracy, two or three (three in all but two instances) different dilutions of each specimen of blood were made up and examined Ten settings of the instrument were made for each dilution The average value of the transmission for the two or three dilutions was then substituted for F in equation (4), the concentration C being the

TABLE 2—*Absorption Ratio for Oxyhemoglobin at Wave Length 542 Millimicrons*

Determination	Absorption Ratio A
1	0.001088
2	1088
3	1097
4	1095
5	1088
6	1090
7	1083
8	1111
9	1080
10	1124
11	1113
12	1103
13	1132
14	1108
15	1093
Average	$0.001,100 \pm 0.000,003$

value found by the van Slyke method The value of D was 1, since containing-tubes 1 cm in length were used The value of the absorption ratio A was then found from the equation

The values obtained for A , the absorption ratio, are shown in table 2 Since fifteen independent determinations were made, and since the probable error is about 3 parts in 1,100, it is believed that the average value of A equals 0.001100 is fairly accurate It was used as the absorption ratio for oxyhemoglobin at wave length 542 millimicrons in all the measurements of hemoglobin concentration reported in this paper Once established, the value of this ratio is, of course, a constant, which can be used in all measurements at the wave length, whatever type of spectrophotometer is used

TESTS OF ACCURACY OF SPECTROPHOTOMETRIC, DARE AND ACID-HEMATIN COLORIMETRIC METHODS

When the value of A had been determined, the hemoglobin concentration for each of the fifteen specimens of blood used in determining A was obtained from a curve, as previously described These values were compared with the van Slyke readings in order to obtain a check on the accuracy of the spectrophotometric method At the same time, each specimen was examined by the acid-hematin colorimetric (Cohen and Smith) and Dare methods in order to obtain first-hand information as to their accuracy A colorimeter of the Duboscq type was used in

the acid-hematin method. Readings on the Dare instrument were made by two different observers, both experienced in colorimetric readings. Each made six settings on the same instrument under identical conditions. The average of each set of six readings was used in obtaining the concentration. Results by all three methods are shown in table 3 and are expressed in percentage variations from the van Slyke results. The values shown are not affected by the scale standards used by the acid-hematin and Dare methods, since all readings were converted to grams of hemoglobin for each 100 cc of blood before comparisons were made.

DISCUSSION OF RESULTS

In order to determine correctly the accuracy of any method of measurement, one must know whether any of the values obtained in the series of measurements were arbitrarily discarded. It is obvious that if the experimenter discards the results which differ widely from the correct value and reports only those which are more accurate, then a correct

TABLE 3—Percentage Variations from van Slyke Readings

Specimen of Blood	Spectrophotometer			Acid Hematin (Cohen and Smith)	Dare	
	Dilution No 1	Dilution No 2	Dilution No 3		First Observer	Second Observer
1	17	13	03	23	13.6	6.3
2	18	13	02	46	15.6	1.9
3	07	01		60	20.1	2.3
4	05	15		13	13.6	5.8
5	18	11	04	12	26.1	16.5
6	15	07	09	04	26.7	11.2
7	16	19	12	12	23.5	20.2
8	06	08	16	10	11.7	3.5
9	23	13	19	14	13.7	0.1
10	21	27	18	18	21.6	14.6
11	16	01	18	27	24.7	12.7
12	00	02	09	33	14.5	7.6
13	33	24	27	14	10.7	4.9
14	30	00	09	77	17.8	10.9
15	11	06	04	05	0.8	12.9
Average		13		25	17.0	8.8
Maximum		33		77	26.7	20.2

idea of the accuracy of the method cannot be obtained from the results published. Again, it is evidently of great importance to the diagnostician to know approximately the maximal error to which the measurements are liable, since that maximal error determines the limit of reliability of the diagnosis in any particular case.

With these principles in mind, it is possible to evaluate the results shown in table 3. No results were arbitrarily discarded in making up the table, that is, the results shown in the table represent an unbroken series of fifteen measurements (actually forty-three measurements by the spectrophotometric method and thirty by the Dare), all results in the series being included regardless of their degree of accuracy.⁶ One may, therefore, take the series as a fairly reliable criterion of the dependability of the methods represented.

⁶ Results in one case were thrown out, but only because the values given by the van Slyke method were not consistent.

From these results the high degree of accuracy of the spectrophotometric measurements is apparent. For all the forty-three independent determinations, the average variation from the results by the van Slyke method is only 1.3 per cent, with a maximal variation of 3.3 per cent. As the individual determinations by the van Slyke method itself may frequently be in error by 1 per cent or more, according to careful check by other experimenters, this agreement must be considered to be close. The maximal error observed probably represents the sum of two errors, that of the van Slyke method and that of the spectrophotometric procedure. The average error should not be affected by the inaccuracies of the van Slyke results, however, since they are probably as often positive as negative. It may be concluded, therefore, that under reasonably satisfactory conditions of measurement it should be possible to measure the concentration of hemoglobin in the blood by the spectrophotometric method with an average error of 1.5 per cent or less, and with a maximal error of about 3 per cent.

Results obtained by the acid-hematin colorimetric method also were found to agree well with the van Slyke results with an average variation of 2.5 per cent and a maximal variation of 7.7 per cent. The errors to be expected, therefore, are roughly twice those indicated for the spectrophotometric method. It is to be noted that the standard solution here used in the determinations for acid hematin was calibrated from the van Slyke readings on the fifteen specimens of blood, so that any inaccuracy of calibration of the standard solution did not affect the accuracy of the results here indicated. The degree of accuracy here shown can therefore be expected only in case the standard solution is accurately calibrated at the time the readings are taken.

The present results agree roughly with those of other experimenters in regard to the inaccuracy of the Dare method (compare with table 1). Not only are the average and maximal errors high, but the two observers do not read the same instrument even approximately the same under identical conditions. In fairness to the method, it should be noted here that in nearly every case the Dare readings were too low. This in itself might indicate only that the instrument used needed recalibration. But inspection of the readings from which table 3 is made up, shows that the errors run from +12.9 per cent to -26.7 per cent. Therefore by recalibration of the instrument it is obviously impossible to reduce the inaccuracy of the method to satisfactory figures. It is clear that if experienced observers do not read the same instrument alike, and if an individual determination, which is the average of six settings of the instrument, may be in error by as much as 20 per cent or more, the instrument is not sufficiently accurate for careful work in diagnosis.

EVALUATION OF THE SPECTROPHOTOMETRIC METHOD

The accuracy of the spectrophotometric method of determining hemoglobin judging from our results appears to be such as to recommend it for practically all purposes. As used in the present investigations, it is also sufficiently simple and rapid to warrant its use in routine measurements. It should prove to be a convenient and accurate method for use in medical research and in the standardization of various instruments and methods.

SIMPLIFICATION OF THE SPECTROPHOTOMETER

The form of spectrophotometer used in the present work is open to the objection that it is expensive. It therefore became our desire to perfect a more simple and inexpensive instrument. For this purpose we chose a Wratten light filter (no. 74 Eastman Kodak Company) which permitted the passage of light of only a reasonably narrow region (from 510 to 550 millimicrons with its maximum at about 530 millimicrons) covering most of the β -absorption band of oxyhemoglobin. The light passing through this filter is not monochromatic, but since it contains those wave lengths which are absorbed in one of the characteristic absorption bands of oxyhemoglobin it may well be used in spectrophotometric measurements of hemoglobin concentration. By the use of this filter and a neutral density wedge for balancing intensities we were able to construct in the rough an instrument which will cost little and which will enable determinations of hemoglobin to be made rapidly and with a fair degree of accuracy. This instrument and some other simple designs are now under investigation.

In this connection, it may be noted that Kennedy⁷ has recently described a method of using light filters in connection with a Duboscq colorimeter in hemoglobin measurements. Also, Exton⁸ presented the results of some similar simplified spectrophotometric methods at the meeting of the Optical Society of America held in Philadelphia, October, 1926.

SUMMARY

Data obtained by various investigators clearly indicate that the Dare, the Sahli and the Tallqvist methods for the determination of hemoglobin are entirely too unreliable for use in making accurate determinations. The evidence concerning the method of Newcomer and that of Cohen and Smith is partly favorable and partly unfavorable.

The object of the present work has been to investigate the possibilities of the spectrophotometric method.

7 Kennedy, R. P. The Use of Light Filters in Colorimetry with a Method for the Estimation of Hemoglobin, *Am J Physiol* **78** 56, 1926.

8 Exton, W. G. A New Method of Colorimetry, *J Opt Soc Am* **14** 134, 1927.

In each of fifteen different specimens of blood the hemoglobin concentration was determined by four different methods, namely, the van Slyke oxygen capacity, the spectrophotometric, the acid-hematin colorimetric (method of Cohen and Smith) and the Dare. In the spectrophotometric method the hemoglobin was converted into oxyhemoglobin and transmission readings were taken at wave length 542 millimicrons. A direct reading spectrophotometer was used, and results were obtained from a cuve without computation. It was first necessary, however, to determine the absorption ratio A for oxyhemoglobin for a wave length of 542 millimicrons. The value of A , the absorption ratio, was found to be $0.001100 \pm 0.000,003$.

Forty-three independent determinations by the spectrophotometric method (no results discarded) gave values having an average variation of only 1.3 per cent from the van Slyke values, with a maximal variation of 3.3 per cent. The method, therefore, is shown to be highly accurate.

Values given by the acid-hematin colorimetric method also agreed fairly well with the van Slyke values, differing on the average by 2.5 per cent, with a maximal difference of 7.7 per cent.

The Dare method was highly inaccurate. This agrees with results by other experimenters. Readings by two different observers differed from the van Slyke readings by 8.8 and 17 per cent on the average, with maximal differences of 20.2 and 26.7 per cent.

We conclude from our investigations that the spectrophotometric method of estimating hemoglobin is not only highly accurate, but also simple and fairly rapid as well. It should prove useful in diagnosis in work of standardization and in research.

A simple and inexpensive form of spectrophotometer, using a color filter and a neutral density wedge, has been tried out and found capable of giving fairly accurate results.

EFFECT OF EXERCISE ON RESPIRATORY EXCHANGE IN HEART DISEASE II^{*}

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AND

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Although breathlessness on exertion is one of the most common symptoms of disease, and though difficulty in obtaining a sufficient exchange of oxygen and carbon dioxide is the underlying cause, the exact mechanism is little understood. Certainly it is the quantity of air and of oxygen relative to the capacity of the subject rather than the absolute amount which is important, and we have tried to learn more about this phenomenon by comparing the reaction of normal and of breathless subjects to the same exercise.

The pioneer work of Haldane has led to an enormous amount of investigation during the last twenty years, and has been applied to the changes at the beginning and end of exercise by Krogh and Lindhard,¹ by Campbell, Douglas and Hobson² and, more recently, by Hill and his fellow workers³. The changes at the beginning take place quickly, and the larger part of the reverse changes take place only a little less quickly when the exercise is stopped. It would be irrelevant to discuss this normal adaptation in detail in this article, but almost at the moment exercise is started, the pulse rate and the rate and depth of breathing are much increased. These take place through nervous influences at first, since, owing to the time taken by the blood in circulation, the chemical factors cannot come into play for some seconds and are not completely in operation for a minute or more, and until then the gaseous exchange gives no true indication of the actual metabolic changes. At the end of exercise all of these drop rapidly at first, then more gradually, and even after mild exercise the return is not complete for two or three minutes. The oxygen intake returns to normal rapidly, and the carbon dioxide output more slowly, so that at this period there is a high respiratory quotient.

Recent work on the blood and respiration in patients who are short of breath from heart disease has been summarized and discussed by

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1 Krogh, A, and Lindhard, J. *J Physiol* **47** 113, 1913, **53** 431, 1919

2 Campbell, J M H, Douglas, C G, and Hobson, F G. *Phil Tr, Lond B* **210** 372, 1920

3 Hill, A V, Long, C N H, and Lupton, H. *Proc Roy Soc Med B* **96** 436, 475, 1924, *ibid B* **97** 84, 155, 1925

Means⁴ and by Meakins and Davies⁵ The most complete information could be obtained on the actual output of the heart per beat and its minute volume, but the different methods are not concordant or easy to use even in healthy subjects, though valuable results have been obtained This method has been tried by Means and Newburgh,⁶ and by Meakins, Dautrebande and Fetter⁷ in valvular disease of the heart, the minute volume having been determined during exercise as well as during rest, and by Barcroft, Bock and Roughton in paroxysmal tachycardia⁸ Means and Newburgh examined a patient with aortic and mitral disease, whose heart was "well compensated", with exercise there was less increase in the minute volume of his blood flow than normally Meakins, Dautrebande and Fetter found that the minute volume even at rest tended to be less than normal and was much less when there was auricular fibrillation, with exercise most of the increase was obtained by increasing the pulse rate

Few studies have been made on the respiratory exchange during and after exercise in patients with heart disease, but observations on young men with valvular disease have been made by Peabody and Sturgis⁹ The exercise used was running upstairs for one minute These authors comment on the delayed fall of ventilation in patients with heart disease, on the delayed elimination of carbon dioxide with a consequent rise of quotient, on the lower percentage of carbon dioxide in the expired air, on the tendency to shallow breathing and increased total ventilation and on the fact that light exercise produced the same percentage of change in both groups, but more subjective dyspnea in the patients

We have obtained a more detailed picture by measuring the respiratory exchange for each minute separately instead of for five minute periods, and by continuing the exercise for five or ten minutes instead of for one minute only, as earlier observations had shown that even three minute exercise was not long enough to obtain equilibrium¹⁰ The easier of our exercises was continued for ten minutes, but as the results showed that five minutes were really long enough to give the information required, the harder exercise was done only for this period The tests chosen were stepping on and off a wooden block 13 inches high six or

4 Means, J H Dyspnea, Baltimore, Williams & Wilkins, 1924, p 79

5 Meakins, J C, and Davies, H W Respiratory Function in Disease Edinburgh, Oliver and Boyd, 1925, p 295

6 Means, J H, and Newburgh, L H Tr A Am Phys **30** 51, 1915

7 Meakins, J, Dautrebande, L, and Fetter, W J Heart **10** 153, 1922

8 Barcroft, J, Bock, A V, and Roughton, F J Heart **9** 7, 1921-1922

9 Peabody, F W, and Sturgis, C C Clinical Studies on Respiration, Effect of Exercise on Metabolism, Heart Rate and Pulmonary Ventilation of Normal Subjects and Patients with Heart Disease, Arch Int Med **29** 277 (March) 1922

10 Campbell, J M H, and Poulton, E P Quart J Med **20** 27, 49, 1926

twelve times a minute. At least three observations were made on each patient at both rates, except in one patient who performed the harder exercise.

The ventilation and metabolism were measured by a closed circuit apparatus of the Regnault-Reiset type developed with the help of Dr E. P. Poulton¹⁰ from similar methods used by Douglas and Haldane,¹¹ Krogh¹² and Benedict.¹³ As we hope to publish a full description shortly, it need not be detailed in this article.

METHOD

Three patients short of breath as a result of heart disease were compared with a healthy medical student, only small numbers were examined, because a more accurate picture could be obtained by taking the average of several observations, and because in any respiratory work, breathing into a mask is always a disturbing factor which can best be eliminated by practice. These four subjects were examined frequently during a period of four months. Young patients with valvular disease of the heart were chosen because this had a relatively simple pathology, and other changes, such as renal or arterial disease, could be readily excluded.

CLINICAL CONDITION OF THE PATIENTS

It is difficult to choose for observation patients in whom there is one simple heart lesion such as might be produced in an experiment on animals. In two of these three cases the lesion was not simple, but this is perhaps less important than it seems at first, because, except for the different type of breathing found in aortic regurgitation and mitral stenosis, it appears to be the degree of the resulting disability rather than its nature which affects the respiratory exchange.

This disability is difficult to express exactly in words, none of these patients belonged to the class in which the cardiac lesion is of such slight importance as to interfere only with heavier work, or to the class in which the onset of cardiac failure has stopped all but the lightest exertion. They belonged to what is perhaps the commonest group of patients with valvular disease, outpatients, for whom walking is fairly easy, but for whom any other than the lightest occupation is impossible and the onset of definite cardiac failure a frequent threat. Two had already had attacks of cardiac failure from which they had made good, if only temporary, recoveries, while in the third, such an attack followed about nine months after these tests. At the time all were able to walk about slowly without much difficulty, but they could not do much more than this.

11 Douglas, C. G., and Haldane, J. S. *J. Physiol.* **44** 305, 1912.

12 Krogh, A. *The Respiratory Exchange in Animals and Man*. New York, Longman, Greene & Co. 1916.

13 Benedict, F. G. *Deutsches Arch. f. klin. Med.* **107** 156, 1912.

A more exact idea will be given by the result of the stepping tests. It should be remembered that, judged by the consumption of oxygen to which this exercise gives rise, it is a little easier to do six of these steps a minute than to walk two and one-half miles an hour, it is more difficult to do twelve steps a minute than to walk three and one-half miles an hour but easier than to walk four miles an hour, and it is more difficult to do eighteen steps a minute than to walk four and one-half miles an hour (Douglas¹⁴). Six steps a minute was easy for all these patients, twelve steps a minute was the first rate which appeared at all difficult. G could not step faster than this, while the other two could start to do eighteen steps a minute but could not continue even for three minutes. The breathlessness seemed greatest in G and least in L. A short clinical history of the three patients follows. Some preliminary results on the ventilation have been recorded in another paper,¹⁵ in which L was referred to as case 11, G as case 12 and A as case 17. The normal person was a medical student (F J S), aged 24, who showed no clinical evidence of heart disease, and who had had no serious illness. He was fit and, though not in training, was taking a moderate amount of exercise.

The pulse rates and other results after these same stepping exercises have been recorded by Hunt and Pembrey.¹⁶

REPORT OF CASES

CASE 1—L, a woman, aged 22, had rheumatic fever in 1913 and was treated in bed for seven weeks. When she left school in 1917, she was engaged in munition work and continued to feel well until 1921, when she again had rheumatic fever. Since then she had suffered from breathlessness and had been unable to work. She had recently coughed up some blood-streaked sputum. On admission to the hospital she was comfortable when at rest, but had a cough and was breathless on exertion. Her heart rate was irregular at the apex between 120 and 130, and at the wrist between 100 and 110. There was a diffuse impulse outside the nipple line, and the area of dullness extended almost to the anterior axillary line and to the right of the sternum. A systolic and a long diastolic bruit were heard at the apex. There were coarse râles at the base of both lungs, but no edema of the feet and no albuminuria.

Auricular fibrillation and mitral stenosis and regurgitation were diagnosed by Dr Hunt. When digitalis was administered the pulse rate soon dropped, and her apex beat came in somewhat. The patient was allowed to be up after five weeks for graduated exercises and was discharged, able to walk about slowly without being short of breath and with an almost regular pulse rate of 70 when at rest. Her condition continued much the same, she attended the outpatient clinic regularly and took digitalis until these observations were made. There was little change in her general condition a year later.

CASE 2—G had rheumatic fever when he was 11 and was twice in the infirmary for eight and six weeks, respectively. He was still short of breath on exertion a year later when these tests were made. The area of dullness extended to the

14 Douglas, C G. *J. Physiol.* **42** 17, 1911.

15 Campbell, J M H. *Guy's Hosp. Rep.* **76** 394, 1926.

16 Hunt, G H, and Pembrey, M S. *Guy's Hosp. Rep.* **71** 415, 1921, **72** 367, 1922.

right of the sternum and half an inch to the left of the midclavicular line. There was a presystolic bruit and thrill at the apex, and the pulse rate at rest was 100 and regular. He did not have edema of the feet. Nine months after these tests, the patient became increasingly short of breath and was admitted to Guy's Hospital under the care of Dr. Beddard, who diagnosed mitral stenosis and regurgitation with heart failure. His pulse was still regular, but the rate had increased to 130. He had edema of the feet, crepitations at the base of the lungs, albuminuria and an enlarged liver. The patient improved under the intravenous administration of strophanthin, but six months later, he was still just able to walk about and was in a much worse condition than when these tests were made.

CASE 3—A, a man, aged 21, gave no history of rheumatic fever. A year before admission to the hospital he had noticed breathlessness, which had gradually become worse. On admission he did not appear to suffer from breathlessness or cyanosis when at rest, but he became breathless on exertion. His pulse was irregular in rhythm and force (between 100 and 120), and some beats felt at the apex were not felt at the wrist. There was visible pulsation over a wide area in the epigastrium and as far as the left anterior axillary line, where the apex could easily be felt in the sixth intercostal space. The area of dulness extended nearly to this line and to the right of the sternum. There were diastolic and systolic bruits at the apex and in the aortic area. There was no edema of the feet and no albumin in the urine. The Wassermann reaction was negative.

Dr. French diagnosed auricular fibrillation, aortic stenosis and regurgitation, mitral stenosis and adherent pericardium. The patient improved on digitalis therapy and was able to get up after a fortnight. He was able gradually to get about the ward without raising his pulse rate above 80 or 90, and was discharged after a month. He attended the outpatient clinics regularly, and graduated exercises were prescribed, but he was not able to progress far with these or to return to work as a vanman, although he was anxious to do so. These tests were made about a year after his discharge from the hospital. His pulse rate was then about 60, and almost regular, under the influence of digitalis, and his apex beat was not displaced so far to the left. Aortic regurgitation seemed to be the outstanding valvular lesion. He died about a year later, but unfortunately the details were not known.

THE OXYGEN INTAKE DURING AND AFTER EXERCISE

The figures for each subject are given in tables 1 and 2, but to make any comparison, allowance must be made for the difference in weight. At rest, metabolism varies with surface area, but the extra metabolism due to exercise varies with the work done, this depends on the body weight, because the height of the step up which the body weight was lifted was the same. The best way to compute the oxygen intake, therefore, was to deduct the metabolism at rest from that during exercise and to express the difference as cubic centimeters per kilogram of body weight. The weight of the normal subject was 75 Kg. and of L, G and A 47.5, 23.8 and 48.2 Kg., respectively.

When this was done, there was surprisingly little difference in the oxygen intake. The normal subject used a little less than the others, especially during the harder exercise. The mechanical work done at both rates was the same, as the easier exercise was continued twice as long, but the extra metabolism for the easier exercise was greater because of the larger number of stepping movements. During the easier exercise, the extra oxygen intakes expressed as cubic centimeters per

TABLE 1—*Metabolism Each Minute with Exercise (Six Steps a Minute)*

Period	Min	Normal Subject (5)†				L (3)†				G (3)†				A (3)†			
		Pulmonary Ventilation, Liters	Carbon Dioxide, per Cent	Carbon Dioxide, Cc	Oxygen, Cc	Pulmonary Ventilation, Liters	Carbon Dioxide, per Cent	Carbon Dioxide, Cc	Oxygen, Cc	Pulmonary Ventilation, Liters	Carbon Dioxide, per Cent	Carbon Dioxide, Cc	Oxygen, Cc	Pulmonary Ventilation, Liters	Carbon Dioxide, per Cent	Carbon Dioxide, Cc	Oxygen, Cc
At rest		6.9	3.39	234	267*	5.9	3.10	183	231*	5.1	2.55	131	167*	8.2	2.40	196	230*
During exercise	1	12.3	3.09	492	550	8.3	3.23	268	433	6.0	2.69	160	250	8.5	3.06	260	417
	2	13.9		550†	600	9.6		341†	483	8.0		210†	267	9.8		330†	517
	3	13.8	4.25	587	720	9.6		380	517	9.1		237	283	11.3		380	533
	4	14.0		598	760	10.1		398	533	10.4	2.41	254	300	12.8	3.40	435	550
	5	14.7	4.31	634	760	10.1	3.98	403	533	10.7		264	317	12.8		470	566
	6	14.5		620	750	10.4		414	533	11.6		270	310	13.9	3.77	497	566
	7	14.7		627	740	10.7		421	550	11.6	2.38	274	310	14.4		497	533
	8	15.2	4.24	645	744	10.7	4.00	428	550	12.0		276	310	14.4		510	550
	9	14.9		630	734	10.4		430	567	12.4	2.23	278	310	14.9	3.77	504	566
	10	15.2	4.21	640	734	10.9	3.96	432	567	13.0		280	310	15.7		520	550
At rest after																	
ward	1	12.0	4.30	518	650	9.9	4.09	405	533	10.0	2.70	270	325	14.7	3.50	516	483
	2	9.5	3.69	351	370	9.3	3.76	350	366	9.6	2.18	238	250	11.2	3.25	364	300
	3	8.2	3.52	288	330	8.0	3.52	282	250	8.4	2.50	210	200	10.1	3.15	318	266
	4	7.5	3.48	262	320	7.7		240	266	7.2	2.49	184	200	9.3	3.07	286	250
	5	7.5		260	320	6.7	3.21	215	250	7.0		180	185	9.6		270	233
	6	7.3	3.45	252	310	6.0		198	217	6.7		168	185	9.1	2.79	254	233
	7	6.9		231	280	6.1		188	217	6.3	2.50	158	167	8.5		230	217
	8	7.3	3.43	249	290	5.9	3.10	183	233	5.6		148	167	8.3	2.63	219	233
	9	6.7		230	260	5.9		182	233	5.4		137	167	8.0		210	217
	10	6.6		226	270	5.9		181	233	5.2	2.53	132	167	8.0	2.58	207	217

* The average barometric pressure and room temperature to correct these figures to standard temperature and pressure are, respectively, 769 and 14 for the normal subject, 765 and 13.5 for L, 760 and 15.5 for G and 765 and 17.5 for A.

† When the carbon dioxide percentage was not determined, the carbon dioxide output was obtained by interpolation.

‡ The number of observations of which these figures are the average. The actual oxygen output would be given more accurately by the curves in figures 1 and 2, as the minute figures were recorded as the pointer passed each 50 cc mark.

TABLE 2—*Metabolism Each Minute During Exercise (Twelve Steps a Minute)*

Period	Min	Normal Subject (3)†				L (3)†				G (1)†				A (3)†			
		Pulmonary Ventilation, Liters	Carbon Dioxide, per Cent	Carbon Dioxide, Cc	Oxygen, Cc	Pulmonary Ventilation, Liters	Carbon Dioxide, per Cent	Carbon Dioxide, Cc	Oxygen, Cc	Pulmonary Ventilation, Liters	Carbon Dioxide, per Cent	Carbon Dioxide, Cc	Oxygen, Cc	Pulmonary Ventilation, Liters	Carbon Dioxide, per Cent	Carbon Dioxide, Cc	Oxygen, Cc
At rest		6.8	3.12	213	260*	6.0	3.13	188	230*	5.1	2.55	131	167*	8.3	2.42	202	232*
Exercise	1	13.2	4.27	562	650	10.5	3.63	381	450	7.2	2.20	158	250	11.5	2.87	330	500
	2	16.3		720†	960	12.9		496†	750	12.0		268†	350	13.1		422†	633
	3	17.9		808	990	13.5	4.02	539	750	14.4	2.28	328	400	15.3	3.25	492	700
	4	19.7	4.38	865	1020	14.0	4.05	568	783					17.6		572	750
	5	20.8	4.39	910	1010	14.8	4.03	600	750					19.0	3.32	632	780
At rest after																	
exercise	1	16.2	4.09	662	730	12.4	4.20	542	783	12.8	2.49	320	400	17.5	3.32	592	645
	2	10.6	3.68	390	480	11.2	3.71	402	466	11.6	2.41	280	300	14.9	3.25	485	412
	3	8.9	3.57	318	380	9.7	3.64	342	366	10.4	2.51	262	250	12.5	3.22	402	333
	4	7.9		277	350	8.5		290	266	8.0		220	200	11.5		352	300
	5	7.2	3.55	256	290	7.7		260	250	6.4		190	200	11.2	2.94	330	288
	6	7.0		247	280	6.9	3.27	230	233	6.4	2.62	168	180	10.9		308	283
	7	7.0	3.39	238	290	6.4		220	225	5.6		146	170	10.1		278	275
	8	6.9		230	280	6.4		210	225	4.8		134	170	9.6	2.68	258	275
	9	6.9		226	250	5.9	3.13	196	225	4.8	2.55	122	160	9.6		252	267
	10	6.4	3.33	221	260	6.4		190	225	4.8		122	160	9.1		232	267
	11	6.3		219	260	5.9		187	233					8.8	2.52	220	250
	12	6.0		217	260	5.6	3.13	185	233					8.8		216	250
	13	6.2		215	260	6.1		184	233					8.5		214	250
	14	6.2		214	260	5.9	3.10	183	233					8.8	2.42	212	250
	15	6.2		213	260	6.1		182	233					8.8		210	250

* The average barometric pressure and room temperature to correct these figures for standard temperature and pressure are 757 and 15 for the normal subject, 757 and 16.5 for L, 763 and 16 for A and 761 and 17.5 for G.

† When carbon dioxide percentage was not determined directly, the carbon dioxide output was obtained by interpolation.

‡ The number of observations of which these figures are the average. The actual oxygen output would be given more accurately by the curves in figures 1 and 2, as the minute figures were generally recorded as the pointer of the dial passed each 50 cc mark.

kilogram were 70 for the normal subject against 73, 75 and 71 for the patients, and during the harder exercise, 58 for the normal subject against 69, 62 and 67 for L, G and A, respectively. The differences were small, and the ability of these subjects to take exercise was but little influenced by the different amounts of oxygen they needed for the same work.

The proportion of this extra oxygen which had to be obtained after the exercise was finished showed a significant difference. At the more rapid rate the normal subject used only 13 cc, while the others used between 20 and 22 cc per kilogram of body weight, in other words, only 23 per cent of the extra oxygen intake of the normal subject, but 30, 35 and 32 per cent of that of the three patients, took place after exercise. The slower rate of exercise was hardly sufficient to bring out this difference.

The relative oxygen intake for the patients can be compared with that for the normal subject in figures 1 and 2, which show the gaseous exchange expressed as cubic centimeters per kilogram. In the normal subject the oxygen intake rose rapidly and had practically reached its maximum by the third minute, indeed, when the exercise was continued for ten minutes, it fell somewhat. At the slower rate there was no significant difference in A, in L, as much oxygen was obtained at the beginning of exercise but more was taken in at the end and for two minutes after, and in G less was obtained at the beginning and more in the first four minutes after the exercise was stopped. At the faster rate the results were more striking, as would be expected from the total figures already given. In A, the oxygen intake was a little less at the beginning of exercise, but toward the end and for ten minutes after the extra consumption of oxygen, it was always slightly greater, in L more oxygen was obtained at the end of exercise and considerably more in the first three minutes after, and in G much less in the first two minutes of exercise and much more in the first four minutes after.

On the whole, there was a slightly greater consumption of oxygen in the patients with heart disease, and a smaller proportion of the oxygen was taken during the exercise, especially during the harder one. While both these changes would tend to increase the breathing, the extent of the change was not sufficient to produce any degree of dyspnea normally.

In these patients it is interesting to compare the oxygen intake during exercise and the work done, as various observers have shown that there is a linear relationship between these two normally (Benedict and Cathcart,¹⁷ Boothby¹⁸ and Lindhard¹⁹). In figure 3, the extra

¹⁷ Benedict, F. G., and Cathcart, E. P. Carnegie Inst. Washington, pub 187, 1913.

¹⁸ Boothby, W. M. *Am. J. Physiol.* **37** 383, 1915.

¹⁹ Lindhard, J. *J. Physiol.* **57** 17, 1922.

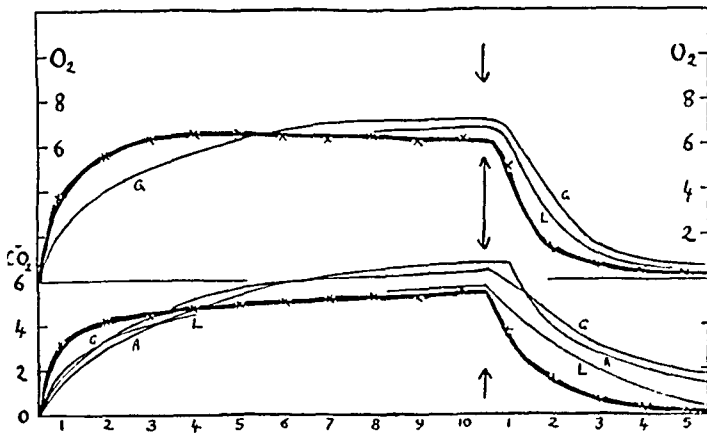


Fig 1—The oxygen intake and carbon dioxide output during ten minutes of light exercise and five minutes after. Extra oxygen and carbon dioxide are shown as cubic centimeters per kilogram of body weight to allow comparison between the four subjects. The upper curves (with the right hand scale) show extra oxygen intake, the lower (with the left hand scale) show extra carbon dioxide output. The thick lines on which separate points are shown as crosses are the curves for a normal subject and the thin are for three patients with heart disease. The arrows indicate the end of exercise. For clarity the curves during exercise are omitted when they are nearly normal, and A's oxygen curve is omitted entirely for the same reason. During the second minute after the exercise, the curves from above downward are those of G, L and a normal person for oxygen and of G, A, L, and a normal person for carbon dioxide. The curves show relatively small changes as regards oxygen intake but some increase after the exercise, and a smaller output of carbon dioxide at the beginning and a much greater output after the exercise is finished.

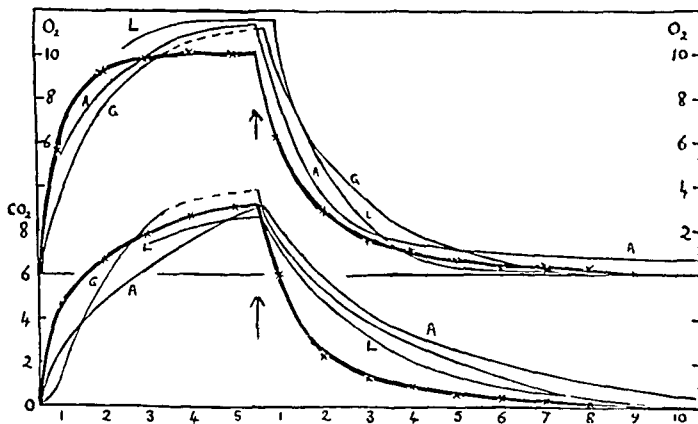


Fig 2—The oxygen intake and carbon dioxide output during five minutes of harder exercise and for ten minutes after. The scale is the same as in figure 1. During the second minute after exercise the curves from above downward are those of G, L, A and a normal person for oxygen and A, G, L and a normal person for carbon dioxide. At this harder exercise the patients' oxygen intake is greater than normal except just at first, and more is taken in after the exercise is finished. The curves for carbon dioxide show a much smaller output at the beginning except for L and a much larger output at the end of the exercise.

consumption of oxygen has been plotted against the work, expressed as kilogram meters per minute, for the normal subject when taking three, six, nine and twelve steps a minute, and for patients when taking six and twelve steps a minute. The curve showing the relationship was practically a straight line, and there was not much difference between the oxygen intake of the normal subject and that of the patients. Owing to the lighter weight of the patients, the work they did for the same rate of exercise was less, but the oxygen intake for the same work was a little more. The line was steeper, showing a faster increase of oxygen intake as the work increased, but the close general agreement meant that the diminished capacity of the patients for increasing their oxygen intake, rather than any change in the metabolism or oxygen requirement, caused breathlessness.

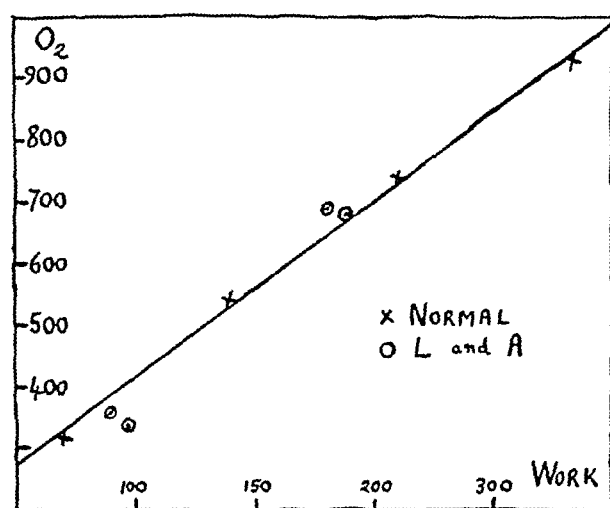


Fig 3—The extra oxygen intake (per minute) for increasing work (as kilogram meters per minute). Oxygen is shown as cubic centimeters per minute and the work done as in kilogram meters. The four points shown for the normal subject represent three, six, nine and twelve steps a minute. The two points shown for each of two patients (whose weight was about two thirds of the normal) represent six and twelve steps a minute. The close agreement between the straight line joining the four points for the normal person and those joining the points for the patients with heart failure shows that it is not any change in the metabolism or the oxygen requirement which is responsible for their breathlessness, but simply their diminished capacity for increasing their oxygen intake.

THE OUTPUT OF CARBON DIOXIDE DURING AND AFTER EXERCISE

All that has been said about the oxygen intake applies with greater force to the output of carbon dioxide. At both rates the amount of carbon dioxide expired relative to the work was always greater in the patients with heart disease than in the normal subject, and, except in one at the slower rate, the difference was always considerable. For the slower rate there was little difference during, but much more after, exercise, the normal subject getting rid of less than 13 per cent of the total after the exercise and the others of 23, 30 and 28 per cent,

respectively, for the faster rate the figures were 25 for the normal subject and 38, 45 and 51 for the patients

If the results are followed from minute to minute (figs 1 and 2), the output of carbon dioxide was more consistent than the oxygen intake. The main difference was the smaller output in all three patients during the first two or three minutes of exercise and the greater output after stopping, sometimes for five minutes, sometimes longer, the increase at the end being much more than the decrease at the beginning. In the normal subject the output reached almost its maximum by the third minute of exercise but continued rising slightly, while after stopping it reached nearly its resting value by the third or fourth minute. At the slower rate the changes were most striking in A and G, L being nearly normal by the fourth minute of exercise and by the fourth minute after stopping. The output was higher in A and G even during the latter part of the exercise. At the faster rate the difference at the beginning was greater, especially in A and G, while after exercise it was greater and lasted longer, being considerable in all three patients five minutes after the exercise was stopped.

The output of carbon dioxide depends on two variables: the total ventilation and the percentage of carbon dioxide in the expired air. At rest the latter was much lower in G and A than in a normal person. The greater output required by the harder exercise was obtained mainly by increasing the ventilation so that there was little difference in the percentage of carbon dioxide. The first minute after the exercise was finished, the percentage was often a little higher, but it then fell to near the resting value at about the same rate as the ventilation.

The behavior of L was most like the normal, as her percentage at rest and her rise during exercise were only a little low and well within normal limits (4 instead of 4.3). In G, whose reaction was most abnormal, the percentage fell steadily throughout the exercise and, as might be expected from this, was lower with the harder than with the easier exercise, namely, 2.2 and 2.4 from 2.55 at rest. This meant that his ventilation had to be increased more than in the others to get an adequate output of carbon dioxide, as was found at both rates of exercise. He could not continue the harder exercise for more than three minutes, and his shallow rapid breathing with such a low percentage of carbon dioxide in the expired air was no doubt closely associated with his greater disability. A occupied an intermediate position. The percentage was as low as in G at rest and was still low during exercise, but the increase was about the same as in health. As his breathing was deeper than normal, this was not even a partial reason for the low percentage of carbon dioxide.

PULMONARY VENTILATION DURING AND AFTER EXERCISE

Little need be said about this, as it has been discussed in a previous paper.¹⁵ The rise and fall of the curves for the ventilation are in general similar to those shown in figures 1 and 2 for the carbon dioxide output. The rate and depth of breathing are given in table 3. In L the breathing was slightly, and in G considerably, more rapid and shallow, while in A it was strikingly deeper and slower, as has been found frequently but not invariably in patients with aortic regurgitation. The probable explanation of the shallow breathing so often occurring with

TABLE 3—*The Rate and Depth of Breathing During and After Exercise*

Time	Min	Exercise Six Steps a Minute (10 Minutes)								Exercise Twelve Steps a Minute (5 Minutes)							
		Normal		L		G		A		Normal		L		G		A	
		Rate	Depth	Rate	Depth	Rate	Depth	Rate	Depth	Rate	Depth	Rate	Depth	Rate	Depth	Rate	Depth
Rest		16	430	19	310	23	220	14	585	16	425	17	355	23	220	14	585
During exercise	1	18	685	19	435	25	240	15	565	18	735	23	455	30	240	13	880
	2	19	730	20	480	31	260	16	610	21	775	22	585	45	265	13	1050
	3	19	725	20	480	36	255	15	750	21	855	21	615	44	330	15	1020
	4	19	735	20	505	37	280	16	800	23	855	22	640			16	1100
	5	19	770	20	505	36	295	14	915	23	910	22	670			18	1060
	6	20	725	21	495	37	310	16	865								
	7	20	735	21	510	38	305	16	900								
	8	20	760	20	535	38	315	16	900								
	9	20	745	20	520	39	320	16	930								
	10	20	760	20	545	41	315	16	980								
Rest after exercise	1	18	670	17	580	32	310	16	920	18	900	19	655	37	345	17	1030
	2	18	530	17	550	31	310	15	750	17	625	18	620	35	300	15	990
	3	18	455	17	470	30	280	13	775	17	525	18	540	33	290	15	835
	4	17	440	19	405	28	255	13	715	17	465	17	500	31	260	15	770
	5	17	440	19	350	26	270	14	685	16	450	18	430	31	205	15	750
	6	16	455	19	315	27	250	13	700	16	435	17	405	31	205	15	725
	7	16	430	20	305	26	240	14	610	16	435	17	375	30	190	14	720
	8	16	455	20	300	26	215	14	590	16	430	19	340	28	170	14	685
	9	15	445	20	295	25	215	14	570	16	430	18	330	26	185	14	740
	10	15	440	20	295	25	210	14	570	16	430	18	355	26	185	14	650

mitral stenosis is in the greater liability to pulmonary congestion, and in several patients one of us has found that the shallow breathing is associated with a greatly reduced vital capacity.¹⁵ Other work on this subject has been discussed in this paper and further observations are being made. The importance of vital capacity in the breathlessness of heart disease has been emphasized by Wentworth and Peabody,²⁰ Hewlett,²¹ Myers²² and others.

20 Peabody, F W, and Wentworth, J A. Clinical Studies on Respiration, Arch Int Med 20 443 (Sept) 1917

21 Hewlett, A W. Heart 11 195, 1924

22 Myers, J A. Vital Capacity of the Lungs, Baltimore, Williams & Wilkins, 1925, p 39

The drum records of the ventilation were characteristic for each patient, and three typical tracings are shown in figure 4. The ventilation of A rose from 8.5 liters at rest to 17.2 liters during the third minute of exercise, and that of G from 5.1 to 14.4. The rate in A rose only from 14 to 17.5, while in G it was already fast at rest and rose from 25 to 43. There was an equally striking difference in the depth of breathing, and these two results were characteristic of what has usually been found in aortic regurgitation and in mitral stenosis, respectively. L, whose disability from mitral stenosis was less severe, occupied an intermediate position. The shallow, rapid breathing of G and the slow, deep breathing of A are well shown in these tracings, as is the sudden increase at the beginning and the slow decrease at the end of the exercise. It is clear that in these patients (as Krogh and

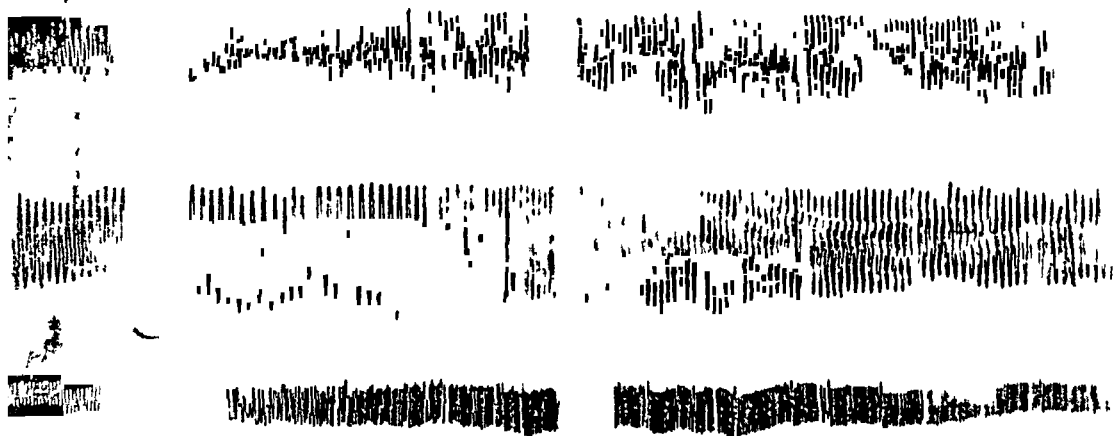


Fig 4—Respiratory tracings before during and after exercise (twelve steps a minute for five minutes) in three patients with heart disease. The record has been cut to show the results of one minute at rest before exercise, the first three minutes of exercise and five minutes of rest after the exercise. The drum was running nearly, but not quite, at the same rate in each subject. The top record is from L with mitral stenosis, the middle from A, whose main lesion was aortic regurgitation, and the bottom from G, with mitral stenosis. The writing point was raised at the end of each minute. The figures for the ventilation and the rate and depth of breathing are given in tables 1, 2 and 3.

Lindhard¹ and others have shown in normal subjects) the increased breathing, practically coincident with the onset of exercise, must have been brought about by the nervous system, while the waning at the end controlled by the more usual chemical stimulus.

RESPIRATORY QUOTIENT DURING AND AFTER EXERCISE

Little change was noted in the respiratory quotient of the normal subject with the exception of a small drop in the second minute of exercise and a corresponding rise toward the end of the harder exercise and in the second minute after stopping the easier one. In patients

at rest the quotient was within normal limits, but at the beginning of exercise it dropped below 0.7 in each case and remained below the normal, except that in A, when he continued to exercise for ten minutes, it rose above 0.9 toward the end, as it did in the normal subject during harder exercise. After stopping, the changes were greater, and in all the patients the rise was higher and lasted longer. This was especially well shown with the harder exercise and with A at both rates, the quotient being above 1.0 for about five minutes. These results are shown graphically in figure 5. Presumably owing to the defective circulation, the carbon dioxide produced cannot be eliminated at the beginning, and the retention leads to increasing breathlessness and to a

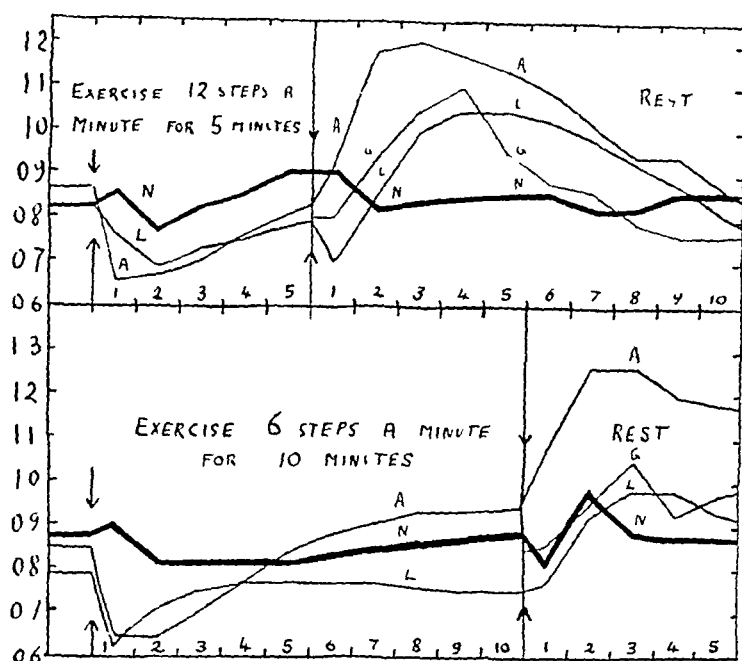


Fig 5—Respiratory quotient during and after exercise. The thick lines are for the normal person, and the thin lines for three patients with heart disease. (For clarity one of these is shown only after the exercise.) The arrows indicate the beginning and end of exercise. In the normal subject there was no great change. In all the patients at the harder, and in A, at both exercises, there was a drop at the beginning of and a considerable rise after the exercise.

slow fall in the ventilation with consequent washing out of carbon dioxide after the exercise is finished.

Taking the total metabolism for the easier exercise and for ten minutes after, the quotient for the normal subject was 0.84, for L, 0.79, and for G, 0.82—figures not far removed from the values at rest—but for A the figure was considerably higher, namely, 0.92. The corresponding figures for the harder exercise were for the normal subject, 0.83, for L, 0.83, for G, 0.8, and for A, considerably higher, 0.9. If the quotients for the extra metabolism are considered after deducting the values at rest, they were hardly different, except for G, in whom they were raised to 0.95 and 0.98, respectively.

SUMMARY AND CONCLUSIONS

A detailed investigation of the effect of exercise—roughly equivalent to slow and ordinary walking—has been made in three patients with heart disease. The metabolism relative to the subject's weight did not vary greatly from the normal, which shows that the capacity for increasing ventilation and circulation, rather than any change in the metabolism or total ventilation required, limits exertion. Throughout the range examined, both of these increased regularly with the work done, so that their relationship could be shown graphically by a straight line.

In these patients the extra oxygen intake as the result of work was only slightly higher than normal. As the exercise became harder the percentage of the extra oxygen required, which had to be obtained at the end of the exertion, increased more in the patients. Both these differences would tend to produce breathlessness, but the degree of change would not have been sufficient to do so in a normal subject.

Greater differences were noted in the elimination of carbon dioxide. At the end of exercise it was retained more than normally, so that the output of this gas and the ventilation fell to their resting values more slowly. The changes at the beginning were similar but less striking. Consequently, the respiratory quotient fell rather more than usual at the beginning and rose considerably more than usual at the end. The percentage of carbon dioxide in the expired air tended to be low, probably because over-ventilation was needed to compensate for defective circulation. In one patient there was practically no rise in the percentage during exercise, so that the whole of the increased output of carbon dioxide had to be obtained by increased ventilation.

The rate and depth of breathing varied in type. In a patient with mitral stenosis it was rapid and shallow. This has been found in several others with mitral stenosis, and is probably associated with the reduced vital capacity and congestion of the lungs to which these patients are liable. The rapid, shallow breathing is itself a further cause of breathlessness. In a patient with aortic disease the breathing was deep and of normal rate. This has been found frequently but not invariably in patients with aortic regurgitation.

Book Reviews

DIE ZUCKERKRANKHEIT UND IHRE BEHANDLUNG By C VON NOORDEN, Geh
Medizinalrat, Professor at the University, Frankfurt, a M, and I Issac,
Professor at the University, Frankfurt, a M Eighth edition Cloth
Price, \$12 40 Pp 627, with 30 illustrations Berlin Julius Springer,
1927

In the ten years that have passed since the appearance of the seventh edition of von Noorden's classic work, revolutionary developments have occurred in the field of diabetes, and these have necessitated a complete revision as well as considerable amplification of the text Much of this development has originated in countries rarely heard from on the subject of diabetes before 1917 The field of activity in the research and therapy of diabetes has been extended to such a degree since 1917 that the German clinicians no longer so completely monopolize the subject It is doubtful, therefore, whether this eighth edition of "Die Zuckerkrankheit" will have as great an influence on American readers as previous editions

The survey of the literature is highly praiseworthy and, although the chapters on dietary management may be prized by many chiefly for their historical interest, the parts of the work bearing on symptomatology and complications must continue to command the greatest admiration A section on the diseases of the eye in diabetes has been contributed by E Grafe This is based on examinations of the eyes in 1,200 cases and represents the most comprehensive study of this subject that has appeared

The chapters on the theory of carbohydrate metabolism deserve careful examination by American students of this subject, particularly because thought in this country has been so largely molded by the school which has taught that the chief fault in diabetes was defective oxidation of sugar Von Noorden has maintained, since 1910, that this teaching is wrong, that the tissues in diabetes oxidize sugar normally, and that the difficulty lies in an oversensitiveness of the liver whereby abnormal amounts of protein and fatty acid are converted into glucose (overproduction of sugar, sugar from fat) The action of the pancreas (insulin) is to check the activity of the liver, inhibit the formation of sugar from protein and fat and stabilize the glycogen stores of liver and other tissues This theory, resting until recently on unsatisfactory supports, has been considerably strengthened by the developments of the last few years Thus Frank Mann's method of resecting the liver, in a two-stage operation which permits the animal to recover from the shock of the operation and makes it possible to obtain dependable respiratory quotients after the resection, has provided evidence that the quotients tend to rise toward unity after hepatectomy The results of his experiments are much more reliable than were those of the earlier experiments of Porges and Salomon This was the original experimental basis of von Noorden's theory, Porges' and Salomon's results being taken to mean that, in the absence of the liver, fat and protein cease to be sources of energy

It has also been demonstrated fairly conclusively in late years that muscular work is accomplished only with carbohydrate This should be credited to A V Hill and Meyerhoff's Nobel prize contributions, curiously, A V Hill's name fails to appear either in the text or in the bibliography If Hill and Meyerhoff's conclusions stand, sugar must be supplied to the muscles from fat whenever the organism is subsisting on materials poor in carbohydrate Recent work of Embden, Lesser and others seems to establish the fact that surviving diabetic tissues in perfusion experiments utilize glucose as well as do the tissues of normal animals, finally, the phenomenon of insulin shock

is readily explained on the overproduction theory, but causes serious embarrassment for those who hold to the view that oxidation is deficient

In discussing the etiology of diabetes, von Noorden and Isaac place great emphasis on heredity, not only heredity for diabetes alone but also heredity of inferiority of the endocrine system as a whole. One member of the system may be affected in one person of a family and another member in the next. Hereditary diabetes in children is not found to be milder than other juvenile diabetes, contrary to the views of Naunyn Loeb and Joslin. Inbreeding, restriction of the field of natural selection, is thought to be the explanation of the high incidence of diabetes in the Jews and high-cast Hindus. An endogenous disposition (abiopathy) is the underlying cause of diabetes, while exogenous factors merely play the role of unleashing (auslosende) agents. Infectious diseases rank first among these. That such exogenous factors, infections, overeating and nervous shocks can cause diabetes in the absence of biologic insufficiency, is considered doubtful.

SULFUR METABOLISM. By MAX KAHN and FRIDERIC G. GOODRIDGE. Price \$9. Pp 800. Philadelphia. Lea & Febiger, 1926.

This work is a compilation of references on sulphur metabolism rather than a review, and this is essentially all that the authors claim for their publication. This volume is comprehensive in scope. The first five chapters are devoted to tables and statements concerning the sulphur content of foods, excreta, secretions, tissues and pigments. The next seven chapters are devoted to data on sulphur metabolism in different animals as affected by age, various physiologic states, drugs and diseases. The following ten chapters are devoted to more detailed discussions and citations on various specific forms of sulphur, such as protein sulphur, lipid sulphur, glucosides, ethereal sulphates and other forms. Brief chapters on hydrogen sulphide as related to biology, on mercaptans, on sulphur bacteria, sulphur in soil and various synthetic sulphur derivatives of possible biologic interest cover the last 200 pages. The concluding chapter covers a brief summary on the methods used for determining total and various forms of sulphur in biologic material. Naturally the discussions are of typical encyclopedic character, and in no sense is the work critical.

TECHNIQUE DE LA REACTION DU BENJOIN COLLOIDAL. Par GEORGES GUILLAIN, professeur a la faculte de medecine de Paris, membre de L'Academie de Medecine, medecin de La Salpetriere et Guy Laroche, medecin des Hopitaux de Paris, P. Lechelle, medecin des Hopitaux de Paris. Paris. Masson & Cie.

This is a small monograph of thirty-four pages, liberally illustrated with curves and four photographic reproductions of reactions. It is simply a report of the technical experiences of the authors covering a large series of observations, the theory and interpretations of the tests are not covered.

The test is based on principles similar to those on which the Lange gold reaction is based, and gives similar results. A much larger series of dilutions is used, generally sixteen, and the resulting curves are therefore more complicated and give promise of being of greater clinical value in the more unusual forms of cerebrospinal syphilis. The tabetic and parietic curves closely resemble the Lange curves.

LOBAR PNEUMONIA

A CLINICAL AND BACTERIOLOGIC STUDY OF TWO THOUSAND
TYPED CASES *

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The biologic classification of pneumococci has been a great stimulus to the bacteriologic study of pneumonia and to efforts directed toward the perfection of an efficient serum treatment for this disease. This classification is a result of the work of several investigators, the chief of whom are Neufeld¹ and Lister² abroad, and Dochez and Gillespie³ in this country. The differentiation of pneumococci into types is based on their capacity to produce specific agglutinins, precipitins and protective bodies. The investigators at the Rockefeller Institute in their original studies found that there were three dominant biologic types of pneumococcus, each possessing specific and characteristic immune reactions. In their experience, the organisms of these three types comprised about 80 per cent of all strains encountered in patients with pneumonia, and represented apparently fixed types of a highly parasitic nature. These three types have been referred to as types I, II and III. In the remaining 20 per cent of their patients they found pneumococci which they referred to collectively as pneumococcus type IV. This group is really an assembly of all other types of pneumococcus, many of them just as distinct as types I, II and III. At first, it was thought that each individual strain of pneumococcus type IV was immunologically distinct, but Olmstead⁴ has shown that certain strains may have common

*From the Second Medical (Cornell) Division and the Pathological Department of Bellevue Hospital. This investigation received financial aid from the Influenza Fund of the Metropolitan Life Insurance Company.

1 Neufeld, F, and Handel. Ueber die Entstehung der Krisis bei der Pneumonie und uber die Wirkung des Pneumokokkenimmunserums, *Archiv f. Klin. u. Exp. Med.* **34** 166, 1910.

2 Lister, F S. Specific Serological Reactions with Pneumococci from Different Sources, *South African Inst. M. Research*, Pub 2, 1913.

3 Dochez, A R, and Gillespie, L J. A Biologic Classification of Pneumococci by Means of Immunity Reactions, *J. A. M. A.* **61**:727 (Sept 6) 1913.

4 Olmstead, M. An Antigenic Classification of the Group IV Pneumococci, *J. Immunol.* **2** 425, 1917.

characters, thus proving that there are definite subgroups in the type IV group of pneumococci. The type IV group is sometimes referred to as the "waste-basket" group, because it contains all pneumococci not included in the three fixed types. Pneumococci of the type IV group are the organisms most frequently encountered in the mouth secretions of healthy persons.

Dochez and his co-workers determined the incidence and death rate for the four so-called types of pneumococcus, and the more recent studies of Avery,⁵ Stillman⁶ and others have thrown considerable light on the epidemiology of the disease with respect to the various types. So far as we know, however, little effort has been made to correlate the type of pneumococcus with clinical manifestations, complications and other features of the disease.

During the past five years more than 2,000 patients with lobar pneumonia have been admitted to the medical wards of the Bellevue Hospital. Through the kind cooperation of the directors of the four medical services, the cases of all patients with lobar pneumonia admitted to the medical wards have been carefully studied from both the bacteriologic and clinical standpoint. With possibly a few exceptions, each person included in this series of 2,000 patients was seen and examined by one of us. A complete résumé of the history of each patient, including pathologic observations in case of autopsy, was kept on large filing cards. On the same card a complete record of the bacteriologic observations, including those made on examination of the sputum, blood culture and during other examinations was also recorded.

SELECTION AND DISTRIBUTION OF CASES

All cases of clinical pneumonia which showed frank signs of consolidation were included in the series. Practically all of these were lobar in type. Such cases were counted even though cultures failed to reveal pneumococci. A few cases of pneumococcus and streptococcus pneumonia were encountered in which the physical signs were not absolutely frank, but in which the patient presented the cardinal symptoms (chill, fever, pain in side and cough with rusty sputum) of lobar pneumonia. They were, therefore, included in the series.

Race and Color—As Bellevue Hospital is a city institution and receives its patients chiefly from the East Side of New York, it was to be expected that all races and practically all nationalities would be represented in this series of cases. Such proved to be the case. The nationality was mentioned in 980 cases. Of these, 40 per cent were born

5 Dochez, A. R., and Avery, O. T. The Occurrence of Carriers of Disease-Producing Types of Pneumococcus, *J. Exper. Med.* **22** 105, 1915.

6 Stillman, E. G. A Contribution to the Epidemiology of Lobar Pneumonia, *J. Exper. Med.* **26** 651, 1916.

in the United States and 15 per cent of these were negroes. Next in frequency were the Irish and Italians, constituting, respectively, 10 and 5 per cent of the total series. The remaining 45 per cent were divided among the various nations of Europe, Asia and South America. Apparently no race is immune to pneumonia.

Occupation—Of 873 patients, the vocation was mentioned on the filing card of 328. Two hundred and twelve of these, or 64 per cent, were engaged in outdoor occupations. Sailors and day laborers led the list and were about equally represented, constituting together more than half of the entire outdoor group. Ninety per cent of the 209 women patients were housewives, and could therefore be classified as indoor workers.

TABLE 1—*Distribution by Age*

Decade	Number of Cases	Percentage of Incidence
Under 20	134	7.1
20 to 30	451	24.1
30 to 40	487	26.0
40 to 50	393	21.0
50 to 60	239	12.7
60 and over	163	8.7

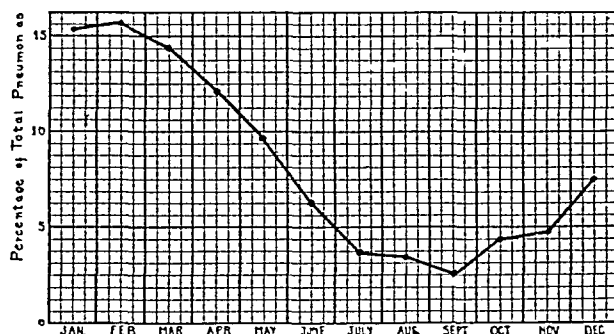


Chart 1—Monthly incidence of cases of lobar pneumonia in Bellevue Hospital

Sex—In 1,867 cases of pneumococcus pneumonia, 1,550 (83.1 per cent) occurred in men, and 317 (16.9 per cent) in women. The incidence rate of pneumonia has always been higher in men than in women, presumably because of their greater exposure to wet and cold. The greater frequency of alcoholism among men also plays some part.

Age—About one half of the present series of cases occurred in patients between 20 and 40 years of age. This was to be expected in view of the fact that the patients in Bellevue Hospital are largely recruited from the laboring classes. The actual incidence percentage for each decade is shown in table 1.

Season—January, February and March are the pneumonia months in New York City. The number of patients (1,195) admitted during

these three months, for the five year period covered by this study, constituted nearly one half of the entire series of cases. The number of admissions for pneumonia for April was distinctly higher than that for December. July, August and September showed the lowest incidence with a total for the three months of only 253 cases. When the incidence of pneumonia by month is plotted (chart 1), there is seen a steady and regular drop in the curve from February to September. In October the curve begins to rise slightly, and continues to rise gradually through the autumn and winter until January, when it takes a sharp rise to the maximum. The actual number of admissions during each month is shown in table 2.

TABLE 2—Incidence per Month

	Cases	Percentage of Incidence
January	406	15.4
February	414	15.7
March	375	14.2
April	311	11.8
May	251	9.6
June	173	6.5
July	93	3.5
August	86	3.2
September	74	2.8
October	113	4.2
November	125	4.7
December	205	7.7
Total cases	2,629	

PREDISPOSING FACTORS AND CAUSES

Etiology—No accurate record was available in respect to the part actually played by exposure, fatigue and other conditions as predisposing etiologic factors. It may safely be said, however, that of such factors, exposure to cold and wet was the most important and was mentioned in the history of a considerable number of the cases. According to the histories, pneumonia followed some acute infection of the upper respiratory tract in 46.7 per cent of the cases of pneumococcus infection. This figure should undoubtedly be higher, as many of the patients were too sick to be questioned carefully. Of 1,002 cases carefully investigated regarding the coexistence of some constitutional disorder, chronic systemic disease, including alcoholism, was found to be a predisposing factor in 32.6 per cent. Alcohol played a rather small part as a predisposing factor. This was probably due to the fact that many of the cases of alcoholic pneumonia were admitted to the alcoholic wards, the material from which was not included in this study.

Exciting Causes Bacteriology—An effort was made to determine the type of infection in every case of pneumonia in the series. This determination was usually made from the sputum. In a few instances, no sputum was available and recourse was had to pharyngeal swabs, blood cultures, pleural fluid or postmortem cultures from the lungs. In certain

severe cases, the type of pneumococcus was determined by performing precipitin tests on the urine. Puncture of the lung was never resorted to in living patients, but was frequently employed after death for the purpose of making a bacteriologic diagnosis, or for controlling cultures previously made from the sputum. Fresh sputum for examination was collected in sterile bottles or Petri dishes. Smears were made and stained by the Gram method, in some cases by Hiss' capsule stain. In all cases in which tuberculosis was suspected a search was made for the tubercle bacillus.

The mouse method was used almost exclusively in the bacteriologic examination of the sputum. Agglutination and precipitation tests were performed with the mouse exudate, and at the same time cultures were made on blood agar plates from both the heart blood and peritoneum of the mouse. Whenever the readings from the mouse exudate indicated pneumococcus type IV or an atypical pneumococcus type II, colonies were fished from the plates, and the pneumococcus was retyped from the

TABLE 3—*Bacteriologic Classification of 2,000 Cases of Lobar Pneumonia*

Bacteria	Cases	Percentage of Incidence
Pneumococcus	1,913	95.65
Hemolytic streptococcus	76	3.8
Friedlander bacillus	8	0.4
Influenza bacillus	1	0.05
Staphylococcus aureus	2	0.1
Total	2,000	

broth culture. Typings from cultures were also made whenever the mouse exudate gave a doubtful reaction. In a majority of the fatal cases, the bacteriologic examination of the sputum was controlled by postmortem cultures. Failure to make a bacteriologic diagnosis was due to lack of sputum, absence of pathogenic bacteria in cultures from the sputum, or death and removal of the body from the hospital before cultures could be taken. Cases in which a satisfactory bacteriologic examination could not be made have been excluded from this series.

In table 3, the 2,000 cases included in the present study have been classified according to the type of micro-organism isolated. In cases of mixed infection the pneumococcus has been given preference, for example, if the sputum showed both pneumococcus and streptococcus, the case has been classified as a pneumococcus pneumonia. Cases in which the pneumococcus was absent and in which the streptococcus was associated with the influenza bacillus have been classified as streptococcic pneumonia.

Of the 2,000 classified cases, 1,913, or 95.65 per cent, showed some type of pneumococcus, 3.8 per cent were apparently due to *Streptococcus hemolyticus*. It is probable that a large number of the latter group

were originally pneumococcus infections, and that the streptococcus, acting as a secondary invader, had entirely replaced the pneumococcus at the time the cultures were taken. Such a transformation in the bacterial flora of the sputum was actually demonstrated in more than one instance. There was one case in which *Bacillus influenzae* was isolated in pure culture from the sputum. Eight cases were due to Friedlander's bacillus, and two cases were apparently caused by *Staphylococcus aureus*. The propriety of considering any case of pneumonia as "lobar" in which no pneumococci are demonstrable is, of course, a question open to much debate. The remainder of this study will be confined almost entirely to the pneumococcic cases.

Table 4 shows the incidence of the various types of pneumococcic pneumonia. Of a total of 1,913 cases of pneumococcic pneumonia, 644, or 33.6 per cent, showed pneumococcus type I, 368, or 19.1 per cent, pneumococcus type II, 268, or 13.3 per cent, pneumococcus type III, and 633, or 33.1 per cent, pneumococcus type IV. When these figures

TABLE 4—Incidence by Type in 1,913 Cases of Pneumococcic Pneumonia

Type of Pneumococcus	Cases	Percentage of Incidence
I	644	33.6
II	368	19.1
III	268	13.3
IV	633	33.1

are compared with those of Dochez and Gillespie, it will be seen that the incidence of type IV pneumonia in the present series is higher than theirs, while that of type II is distinctly lower. The reason for this discrepancy is not clear, but can probably be explained on the basis of a difference in the character of patients studied in the two series.

TYPES OF PNEUMOCOCCUS

Yearly Variations in Incidence—The incidence of the four types of pneumococcus undoubtedly varies within certain limits from year to year. In the present series, for example, the rate of incidence for pneumococcus type I pneumonia was 45.2 per cent during the season of 1920-1921, while for 1922-1923, type I pneumococcus was the cause of only 21 per cent of the cases. The incidence by type for each of the five years covered by this study is shown in table 5.

The incidence of types II and III showed comparatively small variations during the five years of observation. During epidemics of influenza there is always a marked increase in the incidence of pneumococcus type IV pneumonia. This is doubtless due to the fact that postinfluenzal pneumonia is essentially a secondary infection. While the primary infection with the influenza virus comes from without, the secondary infection

is probably autogenous, that is, it is referable to one of the comparatively avirulent strains of pneumococcus type IV which so many healthy persons carry in their own buccal cavities

There is apparently no relation between season and the incidence of the various types of pneumococcic pneumonia. All types occurred in

TABLE 5—*Variation of Yearly Incidence in Pneumococcus Pneumonia*

Period	Type	Cases	Percentage of Incidence
1920-1921	I	166	45.2
	II	68	15.9
	III	51	14.5
	IV	89	23.5
	Total	377	
1921-1922	I	180	33.7
	II	97	18.1
	III	83	15.7
	IV	174	32.5
	Total	534	
1922-1923	I	67	21.0
	II	66	20.6
	III	55	17.2
	IV	131	41.0
	Total	319	
1923-1924	I	85	30.9
	II	55	20.0
	III	44	16.0
	IV	91	33.0
	Total	275	
1924-1925	I	146	35.7
	II	82	20.0
	III	32	7.9
	IV	148	36.2
	Total	408	

TABLE 6—*Incidence of Types in Relation to Age*

Type of Pneumococcus	From 10 to 20 Years		Under 30 Years		Under 40 Years		Under 50 Years		Over 50 Years		Over 60 Years	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
I	79	15.5	216	42.0	323	33.2	535	36.5	92	22.8	32	20.0
II	16	11.9	105	17.9	196	20.2	280	12.2	82	23.9	22	13.7
III	8	5.9	11	7.0	103	10.6	166	11.3	97	24.1	54	33.7
IV	51	38.0	193	32.9	318	33.6	481	32.6	181	32.6	55	34.1
	134	7.1	525	31.3	970	51.9	1,465	78.4	402	21.5	163	8.5

both winter and summer. Streptococcic pneumonia, like pneumonia caused by pneumococcus type IV, is usually a secondary infection, and is, for the most part, a winter and spring infection.

RELATION OF TYPES TO AGE

In table 6 some interesting facts are brought out concerning the relation of age to the incidence of the four types of pneumococcic pneumonia.

According to these figures, young people are particularly prone to pneumococcus type I pneumonia, while the elderly are especially susceptible to pneumococcus type III pneumonia. Type I infections are extremely common in the second decade, constituting 45.5 per cent of all pneumococcic infections occurring in patients between 10 and 20 years of age. In patients under 30, 42 per cent show type I infections. As each succeeding decade is added, the incidence of type I falls, and when the plus sixty group is reached, pneumococcus type I infections constitute only 20 per cent of the entire series. Just the reverse happens with pneumococcus type III. Between the ages of 10 and 20, type III infections comprise only 5.9 per cent of the series. With each succeeding decade, however, the incidence increases, and in the sixty plus group, pneumococcus type III pneumonia constitutes 33.7 per cent of pneumococcic pneumonias occurring at this period of life. In contrast to these two groups, type II and type IV show no special predilection for any age group. The incidence of type IV for the various periods of life is remarkably constant (32.6 to 38 per cent).

TABLE 7—*Incidence of Types in Relation to Sex*

Type of Pneumococcus	Total Men		Total Women	
	Cases	Per Cent	Cases	Per Cent
I	545	35.1	82	25.8
II	312	20.2	50	15.7
III	191	12.5	69	21.8
IV	409	32.2	116	36.6
Total	1,550		317	

INCIDENCE OF TYPES IN RELATION TO SEX

Women constituted only 16.9 per cent of all the cases of pneumococcic pneumonias that were studied. Table 7 shows the relative incidence of the various types in men and in women.

According to these figures, pneumococcus type I is relatively much commoner in men than in women (35.1 per cent against 25.8 per cent). The same is true, but to a less extent, of type II. Type III, on the other hand, is almost twice as common in women as in men, and type IV shows a slight preference for the women (36.6 in women and 32.2 in men).

Incidence of Type in Relation to Age and Sex—When the two factors of age and sex are combined in one table (table 8), their effect on the incidence of the various types is strikingly displayed. For example, type I is three times as common in men under 50 as in women over 50 (37.8 vs. 12 per cent). Type II shows a similar but less striking divergence (19.3 vs. 8.3 per cent). On the other hand, type III is nearly four times as common in women over 50 as in men under 50 (36.1 vs.

10.1 per cent), and type IV is commoner in elderly women than in young men. Summarizing, 57.1 per cent of the cases of lobar pneumonia in men under 50 were either type I or type II, 77.7 per cent of the cases of lobar pneumonia in women over 50 were type III or type IV.

MIXED INFECTIONS

A mixed bacterial flora is not uncommon in pneumonic sputum. The idea is prevalent that mixed infections are associated with bronchopneumonia, usually of the influenzal type, and it is true that most cases of bronchopneumonia showed a mixed bacterial flora. In lobar pneumonia, however, it is not unusual to find the pneumococcus associated in the sputum with some other pathogenic organism. In table 9 the number of pure and mixed infections occurring with each type are compared. These observations are based almost entirely on bacteriologic examinations of sputum.

TABLE 8—*Incidence of Types in Relation to Sex and Age*

Type of Pneumo- coccus	Men Under 50 Years		Women Under 50 Years		Men Over 50 Years		Women Over 50 Years	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
I	462	37.8	73	29.7	83	25.1	9	12.0
II	236	19.3	41	17.9	76	23.0	6	8.3
III	124	10.1	42	17.1	70	21.2	27	36.1
IV	398	32.5	86	35.1	101	36.6	30	41.6
Total	1,220		245		330		72	

TABLE 9—*Incidence of Mixed Flora in 1,913 Cases of Pneumococcus Pneumonia in Relation to Types*

Type of Pneumococcus	Total	Mixed	Percentage of Mixed
I	644	119	18.4
II	368	87	23.6
III	268	64	23.9
IV	633	199	31.2
	1,913	469	24.5

The percentage of mixed infections varies for the types, being lowest in type I cases (18.4 per cent) and highest in the type IV group (31.2 per cent).

Mixed infections are commoner some years than others. For example, the incidence of mixed infections showed a much higher rate in the winter of 1921-1922 than in 1920-1921, possibly on account of the influenza epidemic that appeared in January and February of 1922. The figures are shown in table 10. The incidence of mixed infection was more than four times as common in 1921-1922 as in 1920-1921.

In table 11 the mixed infections are classified according to the bacteria isolated.

By far the commonest mixed flora was that of pneumococcus and the influenza bacillus. Altogether, there were 330 cases of pneumococcal pneumonia that also showed influenza bacilli in the sputum (17.4 per cent). Next in frequency was the combination of pneumococcus with *Streptococcus hemolyticus*. The isolation of two different types of pneumococcus from the same case was an interesting bacteriologic observation. In some instances they were isolated from the same specimen of sputum, in others, from different specimens. When they occurred in the same specimen, one was probably an accidental observation. When in separate specimens, the possibility of a superinfection had to be considered.

TABLE 10—Incidence of Infection According to Seasons

Type of Pneumococcus	Season of 1920-1921			Season of 1921-1922		
	Pure	Mixed	Percentage of Mixed	Pure	Mixed	Percentage of Mixed
I	137	16	10.4	86	82	48.8
II	58	8	12.1	37	55	59.7
III	41	4	8.3	39	37	48.6
IV	68	12	15.0	74	89	54.6
Total	307	40	11.5	236	263	52.7

TABLE 11—Bacteria Found in Mixed Infections

Pneumococcus and Bacillus influenzae	330
Pneumococcus and Streptococcus hemolyticus	82
Pneumococcus, Bacillus influenzae and Streptococcus hemolyticus	28
Pneumococcus, Bacillus influenzae and nonhemolytic streptococcus	5
Pneumococcus type I and pneumococcus type III	1
Pneumococcus type I and pneumococcus type IV	4
Pneumococcus type III and pneumococcus type IV	7
Pneumococcus and tubercle bacillus	4
Pneumococcus and Friedlander's bacillus	9
Total	470

One of the most surprising observations in this connection was the comparatively low incidence of active pulmonary tuberculosis in association with lobar pneumonia. This is consistent with the experience at Saranac Lake and other sanatoriums for the tuberculous, in which lobar pneumonia is rarely encountered among the tuberculous patients. Bronchopneumonia is, of course, often seen as a terminal infection in tuberculosis, but for some reason, frank lobar consolidations are infrequent.

The combination of streptococcus with the influenza bacillus is a common observation in bronchopneumonia, particularly the postinfluenzal type, but is rarely seen in frank lobar pneumonia. *Streptococcus hemolyticus* is probably capable of setting up a true lobar consolidation, though it rarely does so. It is extremely doubtful whether the influenza bacillus ever produces a lobar type of infection. Pneumococcus was

found with both the *Streptococcus hemolyticus* and the influenza bacillus in twenty-eight cases. In nine cases the pneumococcus occurred in association with Friedlander's bacillus. In the latter group, the question arises whether these were genuine mixed infections, or whether the Friedlander bacillus was a purely accidental observation. Indeed, the same question comes up with all the so-called mixed infections (pneumococcus plus tubercle bacillus excepted). Undoubtedly, *Streptococcus hemolyticus* plays an important part as secondary invader in many cases, but the evidence for Pfeiffer's bacillus is not convincing. In respect to death rate and complications, it has been found that the presence of influenza bacilli in the sputum of patients with pneumococcal pneumonia has little effect on either the mortality rate or the incidence of complications.

PRIMARY AND SECONDARY LOBAR PNEUMONIA

Bacteriology—Lobar pneumonia as regards onset can be divided into two large groups—primary pneumonia and pneumonia secondary to some infection of the upper respiratory tract. In making this differ-

TABLE 12—*Relation of Types to Primary and Secondary Pneumonia*

Type of Pneumococcus	Total Cases	Primary Cases	Percentage Primary	Secondary Cases	Percentage Secondary
I	627	401	63.9	226	36.0
II	310	173	55.7	137	44.2
III	209	92	44.0	117	55.9
IV	508	214	42.1	294	57.8
Total	1,654	880	53.2	774	46.7

entiation only those cases could be counted in which a coherent history was obtainable from the patient or from his family. Even under these conditions, the figures are only approximately correct. Patients of low intelligence are often hazy on the subject of coryza and sore throats, and these two conditions are the commonest predisposing infections. Other patients gave a history of a preceding influenza, bronchitis, tonsillitis, otitis media, asthma or pulmonary tuberculosis.

According to table 12, 46.7 per cent of the cases of pneumonia were secondary to some preceding respiratory infection. This figure is probably much too low, but we doubt whether more than 70 per cent, at most, of all cases of lobar pneumonia are secondary infections. If it is assumed that the percentage of error was about the same for the different groups, interesting variations are observed. The incidence of secondary pneumonia is lowest in the pneumococcus type I group (36 per cent), and increases with each group until in group IV 57.8 per cent of the cases are secondary. It was to be expected that secondary pneumonia would occur more frequently in the type III and type IV groups than in the type I and type II groups, as the former are not

uncommonly found as inhabitants of the normal mouth. Pneumococcus type I and type II are almost never encountered in the healthy mouth.

Mixed Infections—If the finding of two different species of bacteria in the sputum of a patient with pneumonia really means a double infection, one would perhaps expect to find the incidence of mixed infections higher in pneumonia secondary to some respiratory infection than in primary pneumonia. Such, however, does not prove to be the case, as is shown in table 13.

In the primary infections 29.8 per cent of the pneumococcic cases showed a mixed flora, while in the cases of secondary pneumonia 27.1 per cent presented more than one species of pathogenic micro-organism.

TABLE 13—*Mixed Flora in Primary and in Secondary Pneumonia*

Type of Pneumococcus	Primary			Secondary		
	Total	Mixed	Percentage of Mixed	Total	Mixed	Percentage of Mixed
I	401	74	18.4	223	45	19.9
II	173	49	28.3	137	38	27.8
III	92	38	41.3	117	26	22.0
IV	214	96	44.8	291	101	34.3
	880	257	29.8	774	210	27.1

TABLE 14—*Incidence of Systemic Disease by Type*

Type	Cases	Systemic Disease	Percentage of Incidence
I	298	61	20.4
II	203	67	33.0
III	131	83	63.3
IV	370	116	31.3
Total	1,002	327	32.6

LOBAR PNEUMONIA IN PATIENTS WITH CHRONIC SYSTEMIC DISEASE

In patients suffering from some chronic constitutional disease, lobar pneumonia may occur as a primary infection or secondary to some preceding respiratory disease. A few of these cases of pneumonia are embolic in origin and develop from septic infarcts. The majority are bronchogenic infections, the sequelae of diminished vitality and resistance.

Incidence of Systemic Disease in Association with the Various Types of Pneumococcus—Table 14 shows the incidence of systemic disease in association with each type. Thirty-two and six tenths per cent of this series occurred in patients with systemic disease. Strangely enough, the incidence of systemic disease was strikingly higher in the type III group than in any of the other groups, being three times as high as it

was in the type I group. It has already been shown that elderly people are particularly susceptible to type III pneumonia. Whether the frequency of systemic disease in the elderly is responsible for this susceptibility is not known, but the figures presented in the foregoing suggest such an explanation. Type III pneumonia is extremely common in institutions for the insane.

CHARACTERISTICS OF DISEASE

Symptomatology—A statistical study of the symptoms of pneumonia as seen in a city hospital is subject to error by reason of the fact that patients are admitted at all stages of the disease. This handicap can be overcome in part by the taking of careful histories, but even then the ignorance of some patients, the inability of others to speak English, the presence of delirium, coma and other factors interfere with the collection of accurate data on the subjective symptoms of the disease.

Day of Admission—A comparatively small number of patients with lobar pneumonia are admitted to Bellevue Hospital during the first forty-eight hours of the disease (from 15 to 20 per cent). The largest number of patients come in on the third and fourth days of their infection.

Character of Onset—The onset of lobar pneumonia is one of the most characteristic features of the disease. In a large majority of cases a diagnosis of pneumonia can be made from a history of the onset alone. As previously pointed out, it may or may not follow an infection of the upper respiratory tract, but in either case, the one quality which distinguishes the onset of pneumonia is its suddenness. There are exceptions, of course, in which the symptoms come on gradually, but in the great majority of cases, the onset of lobar pneumonia is strikingly sudden. The five cardinal symptoms are chill, fever, pain in the side, cough and expectoration of rusty sputum. Of these the chill is usually the first to appear, the pain in the side coming shortly after. Neither the chill nor the pain in the side is present in every case. Fever is present in practically 100 per cent of the cases, though some old people show only a slight elevation of temperature. Cough is present in more than 90 per cent of the cases, but is not always accompanied by rusty sputum. In respect to the other cardinal symptoms, it is interesting to observe how their incidence varied with different types (figures based on the first 1,000 cases of the series).

Pain in the side was mentioned as a symptom in more than 80 per cent of all cases falling in the three fixed groups. The incidence of pain was distinctly lower in the type IV series (approximately 60 per cent).

The chill occurred most frequently in cases of pneumococcus type I (70 per cent), and least frequently in cases of pneumococcus type IV (55 per cent). These figures do not include "chilly sensations."

Rusty sputum is one of the most important signs of lobar pneumonia, not only from the diagnostic, but also from the prognostic standpoint. Its presence is almost pathognomonic, and as long as it persists, one can usually assume that the process in the lungs is still active. Bloody or rusty sputum means engorgement or red hepatization, and as these symptoms represent the earlier stages of infection, it may be safely assumed that blood in the expectoration means an actively extending process. Purulent sputum is usually an expression of gray hepatization or resolution, the latter stages of the infection. The disappearance of rusty sputum is therefore a good omen, if complications can be excluded. Rusty sputum was mentioned in the history or laboratory notes of from 55 to 60 per cent of all the cases in the first three groups—about the same proportion in each group. It was reported in only 40 per cent of the type IV cases. These figures certainly should be higher for all types, but the percentage of error is probably about the

TABLE 15—*Lobes Involved in 1,896 Cases of Pneumococcus Pneumonia*

Type	Right Lower	Right Middle	Right Upper	Left Lower	Left Upper	Two Right Lower	Two Left Lower	Three Right Lower	Right Lower Left Lower	Third Lobes	Four Lobes
I	138	9	36	174	18	59	27	44	88	33	6
II	82	4	29	85	14	37	19	12	74	21	8
III	70	4	11	60	11	20	18	6	59	6	3
IV	150	11	41	186	25	38	29	10	107	22	12
Total	440	28	117	505	68	154	93	72	308	82	29

same in each group. Apparently the incidence of rusty sputum is approximately the same for the three fixed types, with a distinctly lower incidence in the type IV group.

It is hardly necessary, in an investigation of this kind, to enter into a detailed study of the various other symptoms which were observed. There are certain symptoms whose presence is largely dependent on the severity of the infection, such as dyspnea, cyanosis, weakness, delirium. Headache and general muscular aching rarely occur with lobar pneumonia, but are more frequently seen in the influenzal type of pneumonia. Nausea and vomiting are fairly common symptoms and may be due to several causes: toxemia, anoxemia, digitalization or possibly improper diet.

Lobes Involved—In the studies of lobar pneumonia conducted by previous investigators, the right lower lobe has been found to be involved more frequently than any other. In table 15 is shown the lobes involved in the present study.

The left lower lobe was involved more frequently than any other in the infections of a single lobe (505 cases), the right lower lobe coming second (440 cases). The right side, however, was involved more fre-

quently than the left side (1,119 to 974 cases) By far the commonest of the two-lobe infections was the combination of right and left lower lobes (308 cases)

The type of infectious agent appears to bear no relation to the lobe or to the extent of the infection Three and four lobe infections were relatively about as frequent in the milder types (types I and IV) as in the severe types (types II and III of pneumonia)

Pleuritic friction rubs were frequently noted, usually early in the disease and in all types We have no reliable figures for the relative incidence of heaves, flushed cheeks, jaundice, cardiac enlargement and other well recognized physical observations in lobar pneumonia

Leukocytes in Lobar Pneumonia—In almost two thirds of our cases, one or more blood counts were taken during the active stage of the disease A "composite" leukocyte count based on the counts of patients that received no specific treatment shows an initial rise on the first day, averaging about 20,000 leukocytes On the second day the count is

TABLE 16—Results of Blood Cultures in 329 Cases of *Pneumococcic Pneumonia*

Type of <i>Pneumococcus</i>	Number Cultured	Number Positive	Percentage
I	125	33	26.4
II	75	31	39.7
III	36	10	27.7
IV	90	15	16.6
Total	326	89	24.0

higher, and on the third day the peak is usually reached After the third day, the counts are lower but still considerably above normal In a monkey with experimental pneumococcic pneumonia, the peak is often reached on the second day of the disease, and the same may happen in the case of man

In fatal cases with septicemia the leukocyte count in both monkey and man is usually below normal, especially toward the end, unless a complication is present, in which case there may be a secondary rise in the curve

Pneumococcic Bacteremia—Blood cultures were taken in 329 cases in this series

Technic—In most cases from 1 to 5 cc of blood was drawn directly into plain broth One cubic centimeter was plated out in agar in order that the number of colonies per cubic centimeter of blood could be determined

Of the 329 cases in which cultures were taken, eighty-nine, or 24 per cent, showed some type of pneumococcus in the blood The incidence of septicemia was much higher (34.5 per cent) in 107 cases in which cultures were taken repeatedly during the course of the disease

(table 25) As might have been expected, the incidence of septicemia was higher in the severe types (II and III) than in the mild types (I and IV) Type II pneumonia is essentially the pneumonia of septicemia, yielding positive blood cultures more than twice as frequently as type IV infections

Urinalysis and Roentgen-Ray Examination—Practically every case showed albumin with or without casts at some stage of the disease In only a small percentage of the cases studied in this series were the patients examined by roentgen ray The number was too small for analysis

COURSE OF DISEASE

No striking features in the clinical course could be demonstrated as characteristic of the various types of pneumonia The temperature is more apt to be irregular in type IV pneumonia than in the three fixed

TABLE 17—*Duration of Disease in Untreated Patients Who Recovered*

Type	Cases	Average No. of Days
I	264	88
II	117	86
III	87	91
IV	226	87
Total	692	88

TABLL 18—*Incidence of Crisis and Lysis in Untreated Patients*

Type of Pneumococcus	Total Cases	Crisis	Lysis	Percentage With Crisis
I	285	116	112	56.6
II	122	61	61	50.0
III	89	35	54	39.3
IV	246	113	155	45.5
	744	335	362	49.6

types of infection, in which a high and fairly level plateau is the general rule However, there are numerous exceptions in all groups

Duration of Disease—It was interesting to compare the duration of pneumonia (as measured by fever) for the various types Table 17 shows the average duration for each type, dating from the day of chill or pain in the side to the first day of a rectal temperature of 100 F or less The figures are based on a series of 692 consecutive cases, in none of which the patient was treated with serum Cases in which complications developed have been excluded

Pneumococcus type III pneumonia runs a somewhat longer course than the other types This characteristic was even more strikingly evident in our studies of experimental pneumonia in monkeys

Mode of Termination—Lobar pneumonia terminates by either crisis or lysis Table 18 shows the incidence of crisis and lysis for each type

in 717 cases of pneumonia in which the patient received no specific treatment

Crisis occurred most frequently in type I infections (56.6 per cent). The incidence of crisis in type III was much lower, only 39.3 per cent. Types II and IV occupied intermediate positions.

DEATH RATE

The death rate in pneumonia is dependent on a great many factors. A number of these factors will be considered with special reference to the influence of pneumococcus type.

Effect of Season on Death Rate—Before analyzing the effect of the pneumococcic type on the death rate of pneumonia, it may be worthwhile to show how the mortality rate in pneumonia is affected by season.

TABLE 19—Percentage Mortality by Month

Month	Cases	Died	Percentage Fatal
January	406	152	37.4
February	414	160	38.6
March	375	109	29.0
April	311	90	28.9
May	254	61	24.0
June	173	33	19.0
July	93	26	27.9
August	86	18	20.9
September	74	25	33.7
October	113	43	38.0
November	125	40	32.0
December	205	68	33.1
Total	2,629	825	31.7

In table 19, the incidence of pneumonia by month, with the number of deaths, is indicated for a period covering about five years. In this table, it will be seen that there is a considerable difference in the death rate between the group of cases which occurred during the season that pneumonia was most prevalent (January, February and March) and the group of cases that occurred during the season that it was least prevalent (July, August and September). In the former group of 1,195 cases, the death rate was 35.2 per cent, whereas, in the latter group of 253 cases, the death rate was only 27.2 per cent, 8 per cent less than that for the winter months. Pneumonia, therefore, is not only more frequent in the winter, but appears to be more serious also. This may be due to several factors, such as increased virulence of the organism or lower resistance of the patient.

Variation in Mortality by Year—In the Bellevue Hospital, the death rate for pneumonia has shown considerable variation from year to year. For instance, in the season of 1920-1921 the death rate was only 24.6 per cent, whereas, in the season of 1923-1924, the death rate was 34.9 per cent, an increase of 10 per cent. This variation in death rate

from year to year does not appear to be dependent entirely on variations in the incidence of types. So many factors enter into the problem that it would be dangerous to say which of them exercises the dominant influence in determining the death rate for any particular season.

Death Rate According to Type—Table 21 shows the death rate for the various types. As each group consists of a hundred or more

TABLE 20—Variations in Yearly Mortality Rates

Period	Type	Patients Died	Percentage of Mortality
1920-1921	I	34	20.4
	II	29	29.4
	III	19	35.2
	IV	20	22.4
	Total	93	21.6
1921-1922	I	21	17.1
	II	38	39.3
	III	36	43.3
	IV	33	18.9
	Total	138	25.8
1922-1923	I	8	11.0
	II	26	32.8
	III	22	40.0
	IV	33	25.1
	Total	89	27.9
1923-1924	I	17	20.0
	II	28	50.9
	III	20	45.4
	IV	21	34.0
	Total	86	34.9
1924-1925	I	32	21.9
	II	34	41.4
	III	17	53.1
	IV	45	50.4
	Total	128	31.3

TABLE 21—Death Rate According to Type in Pneumococcic Pneumonia

Type of Pneumococcus	(No Specific Treatment) Cases	Died	Per Cent
I	352	73	20.7
II	221	93	42.0
III	161	67	41.6
IV	373	109	29.2
	1107	342	30.8

cases, these figures should be reliable. Only those patients have been included in this table who received no specific therapy.

The death rate for type I pneumonia, even when no serum is given, is lower than that of any of the other types. No doubt this low figure (20.7 per cent) is due in large measure to the fact, previously brought out, that type I pneumonia is the pneumonia of young people. This figure is considerably lower than that given by Cole⁷ for type I pneumonia (not treated with serum) at the Rockefeller Institute.

⁷ Cole, R. Nelson's Loose-Leaf Living Medicine 1 203, 1920

The death rate for 221 cases of pneumococcus type II pneumonia in our series was 42 per cent, in other words, it proved to be the most virulent of the four types. Our figure is much higher than that of Cole, whose series of cases of type II pneumonia showed a death rate of only 29.5 per cent. After extensive experience with type II pneumonia, we have come to look on it at Bellevue as the most serious form of pneumonia with which we have to deal, and the reason for this is that nearly half of the patients develop a pneumococcic bacteremia. Even allowing for the fact that pneumonia at Bellevue Hospital shows a somewhat higher death rate than that observed in other hospitals, it is probable that Cole's figure of 29.5 per cent is too low.

The death rate for 161 cases of pneumococcus type III pneumonia in our series was 41.6 per cent, almost identical with that observed in the Rockefeller series (44.3 per cent). As we have pointed out previously, it appears that the high death rate in pneumococcus type III is largely dependent on the fact that type III pneumonia is essentially the pneumonia of elderly people. Type III pneumonia in the young is not particularly severe.

The death rate for 373 cases of pneumococcus type IV pneumonia was 29.2 per cent. Type IV pneumonia, like type III, is not necessarily a virulent infection. The death rate for type IV pneumonia in the Rockefeller series was only 13.2 per cent. The number of cases, however, on which this figure is based is not mentioned. The death rate in type IV pneumonia, as in other types, will depend in large part on the kind of patients with which one is dealing, but in our experience, the prognosis in type IV pneumonia is not so good as it has been reported to be, largely because it is the type of pneumonia most frequently seen after influenza and also as a complication of various chronic systemic diseases.

The death rate for the entire series of 1,107 cases of pneumococcic pneumonia in which the patient received no specific treatment was 30.8 per cent, a figure which corresponds rather closely to the usual death rate for lobar pneumonia in city hospitals everywhere.

From these mortality figures, it is evident that types I and IV are the mild forms of pneumonia, while types II and III are almost twice as virulent. In spite of these differences, however, there are more deaths from type I and type IV pneumonia than there are from the type II and III infections, because the mild forms are of so much commoner occurrence.

Mortality in Relation to Age and Type—The importance of age in the prognosis of pneumonia has long been recognized. In table 22 the relation of age to mortality in the various types of pneumonia is clearly brought out.

It will be observed that in patients under 40 years of age, type III pneumonia is a comparatively mild infection, showing a death rate actually lower than some of the other types. After 40, the death rate for type III becomes high, no higher, however, than that for type II cases in the same age group. All four of the types show a steadily increasing death rate for each decade. This increase in the death rate for each decade is well shown in the total number of cases for each age group. Starting with a mortality rate of 11.1 per cent for patients under 20, it increases steadily with each decade until, in the group of patients over 60 years of age, it has reached a figure of 52.7 per cent.

TABLE 22—Mortality in Relation to Age and Type

Type of Pneumococcus	Under 20 Years		20 to 30 Years		30 to 40 Years		40 to 50 Years		50 to 60 Years		Over 60 Years	
	Per centage		Per centage		Per centage		Per centage		Per centage		Per centage	
	Cases	Fatal	Cases	Fatal	Cases	Fatal	Cases	Fatal	Cases	Fatal	Cases	Fatal
I	59	8.4	187	16.0	179	17.8	110	21.0	60	26.6	32	31.2
II	16	18.7	89	17.9	91	38.4	84	5.5	69	45.0	22	63.6
III	8	12.5	53	15.1	62	29.0	63	44.4	13	69.7	54	59.2
IV	51	13.6	112	13.3	155	21.2	136	29.4	76	38.1	55	34.5
	134	11.1	451	15.5	487	21.2	393	34.8	239	42.7	163	52.7

TABLE 23—Incidence of Positive Blood Cultures in Relation to Type and Outcome

Type of Pneumococcus	Patients That Recovered			Patients That Died		
	Positive Percentage			Positive Percentage		
	Cases	Blood Culture	Positive	Cases	Blood Culture	Positive
I	87	9	10.3	8	24	63.1
II	39	3	7.6	56	28	77.7
III	17	2	11.1	19	8	42.1
IV	64	1	1.5	26	14	53.8
	207	15	7.2	119	74	62.1

Relation of Septicemia to Death Rate—Septicemia has a pronounced effect on the prognosis in pneumonia. In table 23 the incidence of septicemia in relation to outcome is indicated for the various types. The figures in this table include all cases in which one or more blood cultures were taken during the course of the disease.

In 207 patients that recovered, bacteremia was demonstrated in only 7.2 per cent. In the sixty-four patients with type IV pneumonia that recovered, only one showed a positive blood culture.

In contrast to these figures, 119 patients that died showed pneumococcus bacteremia in 62.1 per cent. In each of the four types the incidence of bacteremia was many times higher in the fatal cases than in those in which the patient recovered.

In table 24, the same fact is brought out in a slightly different way. The death rate in cases that did not show septicemia is compared with the death rate in cases that showed septicemia. Here, again, a striking difference is noted. Two hundred and forty patients whose blood remained sterile showed a death rate of only 18.7 per cent. On the other hand, eighty-nine patients with positive blood cultures showed a death rate of 83.1 per cent.

As regards the different types, it will be seen that septicemia in types II, III and IV nearly always indicates a fatal termination, the death rate being approximately 90 per cent for these groups. The outlook in type I cases with septicemia is not so grave, otherwise, type I

TABLE 24—*Death Rate in Cases with Sterile Blood Cultures*

Type of Pneumococcus	Death Rate in Cases With Sterile Blood Cultures			Death Rate in Cases With Positive Blood Cultures		
	Cases	Fatal	Per Cent	Cases	Fatal	Per Cent
I	92	14	15.2	33	24	72.7
II	47	8	16.2	31	28	90.3
III	26	11	41.5	10	8	80.0
IV	75	12	16.0	15	14	93.3
	240	45	18.7	89	74	83.1

TABLE 25—*Relation of Bacteria to Death Rate in Pneumonia*

Types of Pneumococcus	Cases Studied	Cases Showing Positive Blood Cultures		Cases Showing Sterile Blood Cultures	
		Cases	Deaths	Cases	Deaths
I	39	11	6	28	3
II	22	14	13	8	1
III	11	4	3	7	1
IV	55	8	7	27	2
Total	107	37	29 or 78.3%	70	7 or 10%

differs in no respect from the other types, insuring an extremely high death rate among patients who develop pneumococcic septicemia.

The figures presented in tables 23 and 24 are open to one serious criticism in that many of the patients had only one or two blood cultures taken during the course of their disease. Some of these patients may have had a bacteremia before or after the culture was taken.

In table 25 more accurate figures are presented in a series of 107 patients in whom blood cultures were taken at frequent intervals during the course of the disease, in some instances every day.

It will be observed that in all four types the death rate was high in cases in which there were positive blood cultures. The death rate was somewhat lower in the septic type I series than in the other three types, but this difference was probably due to the effect of specific therapy. Furthermore, it will be noted that the incidence of positive blood

cultures in the various types is roughly proportional to their respective death rates. The occurrence of bacteremia in the less virulent type I and type IV infections is comparatively low, while in the more severe type II and type III infections the incidence of bacteremia is distinctly higher. Finally, the total mortality rate for thirty-seven patients with pneumococcic pneumonia and with positive blood cultures was 78.3 per cent, in contrast to a death rate of 10 per cent for seventy patients with sterile blood cultures.

Effect of Systemic Disease on Death Rate—The death rate in pneumonia is greatly increased when the disease occurs in patients already affected with some chronic systemic disease.

TABLE 26—*Death Rate for Cases Showing Systemic Disease*

Type	Cases	Died	Percentage Fatal
I	61	23	37.7
II	67	38	56.7
III	8	7	87.5
IV	116	39	33.6
Total	327	155	46.4

TABLE 27—*Death Rate for Cases without Systemic Disease*

Type	Cases	Died	Percentage Fatal
I	237	37	14.3
II	100	50	50.0
III	48	4	8.3
IV	291	70	23.5
Total	675	161	23.4

In table 26, the death rate for 327 cases of pneumococcic pneumonia associated with systemic disease was 46.4 per cent, a figure greatly in excess of the normal death rate. Furthermore, the death rate for every type was affected. Even in type IV cases, one third of all the patients infected died.

On the other hand, the death rate in cases entirely free from systemic disease was distinctly lower than the usual figure.

In table 27, it will be observed that in a series of 675 cases of pneumonia without systemic disease, the death rate was only 23.4 per cent. The surprising feature about this table is the extremely low death rate in the type III series. In forty-eight cases of type III pneumonia without systemic disease, there were only four deaths, a mortality rate of 8.3 per cent. It has been pointed out earlier in this study that patients with chronic systemic disease are particularly susceptible to type III pneumonia. It is clear, however, that when healthy persons are attacked by the type III pneumococcus, their chances of recovery are excellent.

Relation of Death Rate to the Number of Lobes Involved—As might be expected, the death rate in pneumonia runs parallel with the number of lobes involved

In single lobe infections, the death rate in the present series was only 20·9 per cent, in two lobe infections, 36·3 per cent, in three lobe infections, 40·8 per cent, in four lobe infections, 65·5 per cent. This increase in death rate with the number of lobes affected applies to all four types of pneumonia

TABLE 28—*Mortality and Lobe Involvement in 1,896 Cases of Pneumococcus Pneumonia*

Type	Single Lobe			Two Lobes			Three Lobes			Four Lobes		
	Cases	Died	Per-centage	Cases	Died	Per-centage	Cases	Died	Per-centage	Cases	Died	Per-centage
I	375	51	12·6	174	43	18·7	77	21	32·3	6	4	33·3
II	214	70	29·6	110	48	37·2	33	16	42·1	8	5	60·0
III	156	55	29·7	97	46	35·9	12	8	50·0	3	1	25·0
IV	413	67	15·5	174	65	36·1	32	18	58·6	19	9	57·1
Total	1,158	243	20·9	555	202	36·3	154	63	40·8	26	19	65·5

TABLE 29—*Incidence of Pneumococcus Complications in Relation to Type*

Type of Pneumococcus	Cases	Em-pyema	Peri-car-ditis	Endo-car-ditis	Menin-gititis	Arth-ritis	Phle-bitis	Peri-tonitis	Total	Percent-age of Incidence
I	644	44	4	4	14	5	6	1	78	12·1
II	368	13	3	2	6	0	2	0	26	7·0
III	268	10	1	0	3	1	1	1	17	6·3
IV	633	32	2	4	9	2	4	1	54	8·5
	1,913								175	9·1

COMPLICATIONS

Complications in pneumonia are proverbially common. Any sort of an analysis of the complications which occurred in the 2,000 cases of pneumonia included in the present study would constitute an extensive treatise in itself. In the present report, we have limited our observations to the commoner and more serious complications. These are usually caused by the pneumococcus, but occasionally the streptococcus is responsible, when it occurs as a secondary invader.

Incidence of the More Serious Complications in Relation to Type—In 1,913 cases of pneumococcic pneumonia, serious complications occurred 175 times, an incidence of 9·1 per cent. In table 29 the incidence of the various complications are listed according to type. When two complications developed in the same case, both have been listed.

The striking feature of table 29 is the high incidence of complications in pneumococcus type I pneumonia, 12.1 per cent of the type I cases being complicated by empyema, pericarditis or one of the other severe complications. The other three types developed complications with about equal frequency, 7.63, and 8.5 per cent, respectively. Empyema was by far the commonest complication in all types. Next in frequency came meningitis. The other complications were comparatively rare.

Empyema—Pneumococcus type I pneumonia showed the highest incidence of empyema—6.8 per cent. The next highest incidence was for type IV (5 per cent), while type II and type III showed an incidence of 3.5 and 3.7 per cent, respectively. The death rate for the entire group of patients with empyema was 38.3 per cent, with only slight

TABLE 30—*Incidence and Mortality of Empyema in Relation to Type*

Type of Pneumococcus	Total Cases	Cases of Empyema	Percentage of Incidence	Deaths	Death Rate Percentage
I	644	44	6.8	16	36.3
II	368	13	3.5	5	38.4
III	268	10	3.7	3	33.3
IV	633	32	5.0	14	43.7
Total	1,913	99	5.1	38	38.3

TABLE 31—*Relation of Time of Onset of Empyema to Death Rate*

Onset	Number	Died	Mortality Percentage
Before seventh day	11	10	90.0
Seventh to fourteenth day	27	14	51.8
On and after fourteenth day	61	41	22.9
	99	38	38.3

differences for the various types. It is possible that the high incidence of empyema and other pneumococcus complications in type I pneumonia is dependent on its high prevalence in young people.

An interesting relationship between the mortality rate and the time of development of empyema is shown in table 31. The earlier in the disease the empyema develops, the higher the death rate. In patients that developed empyema before the seventh day of the disease the rate of mortality was extremely high (90 per cent). When empyema developed between the seventh and fourteenth day after the onset of pneumonia the death rate was 51.8 per cent. In patients that developed empyema after the fourteenth day, the death rate was only 22.9 per cent. Fortunately, the last group is the largest, constituting nearly two thirds of the entire series. It is particularly in streptococcus pneumonia that empyema develops early, and this fact doubtless accounts in great measure for the high death rate associated with this form of pneumonia. With the

exception of a few patients in whom empyema was diagnosed just before or after death, patients who developed empyema were transferred to the surgical service for thoracotomy. Patients who developed empyema early in the disease were treated by aspiration until their condition warranted surgical intervention.

COMMENT

The analysis of a large group of cases of pneumococcic pneumonia has enabled us to make some interesting and probably safe deductions concerning certain clinical features of the various types. In the course of our studies at Bellevue, a number of these type characteristics were suspected long before statistics were available to prove them. The fact that the various types of pneumonia possess certain characteristics that differentiate them from one another serves to emphasize the importance of the bacteriologic study in every case. The time has come when every case of lobar pneumonia should be typed. This can usually be accomplished by injecting some sputum into a mouse. If sputum is not available, washings from a throat swab should be injected. Blood culture should also be taken, and precipitin tests carried out on the urine.

Just why these differences exist between the four types of pneumococcic pneumonia it is impossible to say. It is difficult to understand why young people should be particularly susceptible to pneumococcus type I while older people are more readily attacked by pneumococcus type III. It is difficult to explain why serious complications are almost twice as common in type I as in the other types, or why type II and type III pneumonia are almost twice as fatal as type I or IV. Nevertheless, these differences in the types do exist, and it is important for the practitioner to be aware of them. Knowing the type of pneumonia with which he is dealing, the physician at once knows a good deal more about his patient, his chances of recovery, the danger of complications and the feasibility of specific treatment. For these reasons, an exact knowledge of the bacterial nature of the infection has become an indispensable requisite in the treatment of a pneumonic patient.

In this study we have purposely refrained from a discussion of our results with specific and nonspecific therapy. Approximately one third of the 2,000 patients composing this material received some form of specific or nonspecific treatment. A few patients received anti-pneumococcus serum; a large number received Huntoon's pneumococcus antibody solution; a much smaller number were treated with Felton's concentrated antipneumococcus serum. Specific treatment was not

The striking feature of table 29 is the high incidence of complications in pneumococcus type I pneumonia, 12.1 per cent of the type I cases being complicated by empyema, pericarditis or one of the other severe complications. The other three types developed complications with about equal frequency, 7.63, and 8.5 per cent, respectively. Empyema was by far the commonest complication in all types. Next in frequency came meningitis. The other complications were comparatively rare.

Empyema—Pneumococcus type I pneumonia showed the highest incidence of empyema—6.8 per cent. The next highest incidence was for type IV (5 per cent), while type II and type III showed an incidence of 3.5 and 3.7 per cent, respectively. The death rate for the entire group of patients with empyema was 38.3 per cent, with only slight

TABLE 30—*Incidence and Mortality of Empyema in Relation to Type*

Type of Pneumococcus	Total Cases	Cases of Empyema	Percentage of Incidence	Deaths	Death Rate Percentage
I	644	44	6.8	16	36.3
II	338	13	3.5	5	38.4
III	268	10	3.7	3	33.3
IV	633	32	5.0	14	43.7
Total	1,913	99	5.1	38	38.3

TABLE 31—*Relation of Time of Onset of Empyema to Death Rate*

Onset	Number	Died	Mortality Percentage
Before seventh day	11	10	90.0
Seventh to fourteenth day	27	14	51.8
On and after fourteenth day	61	41	22.9
	99	38	38.3

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limited to any one type of pneumococcic pneumonia. Our results with these various agents have been reported in other articles⁸

SUMMARY

A summary of the more important facts derived from this investigation may be stated as follows

A bacteriologic classification of 2,000 typed cases of lobar pneumonia showed the following distribution of pathogenic organisms: pneumococcus, 95.65 per cent, hemolytic streptococcus, 3.8 per cent, Friedländer's bacillus, 0.4 per cent, influenza bacillus, 0.05 per cent, and *Staphylococcus aureus*, 0.1 per cent.

The incidence of the various types of pneumococcus was as follows: pneumococcus type I, 33.6 per cent, pneumococcus type II, 19.2 per cent, pneumococcus type III, 13.4 per cent, pneumococcus type IV, 33.1 per cent. There was considerable variation from year to year in the incidence of the various types.

A study of the relation of types to age shows that young people are particularly prone to pneumococcus type I infections, and elderly people to pneumococcus type III. Type II and type IV show no special predilection for any age group.

A study of the incidence of type in relation to sex shows that type I and type II are commoner in men than in women. Type III and type IV are commoner in women than in men. Type III is almost twice as common in women as in men. Type I pneumonia is three times as common in men under 50 as it is in women over 50. On the other hand, type III pneumonia is more than three times as common in women over 50 as it is in men under 50.

The percentage of mixed infections among the cases of pneumococcic pneumonia is lowest in type I cases (18.4 per cent) and highest in the type IV group (31.2 per cent). The incidence of mixed infections varies from year to year, being highest during years when influenza is prevalent. By far the commonest mixed infection was that of the pneumococcus in association with the influenza bacillus. The pneumococcus and hemolytic streptococcus is the next most frequent combination.

The incidence of preexisting systemic disease is highest in the pneumococcus type III group, 63.3 per cent of all type III infections occurring in patients with systemic disease.

The type of pneumococcus appears to bear no relation to the lobe involved or to the extent of the infection. Three and four lobe

⁸ Cecil, R. L., and Larsen, J. P. Clinical and Bacteriologic Study of One Thousand Cases of Lobar Pneumonia, *J. A. M. A.* **79**: 343 (July 29) 1922. Cecil, R. L., and Baldwin, H. S. The Treatment of Lobar Pneumonia with Subcutaneous Injections of Pneumococcus Antibody Solution, *J. Pharmacol. & Exper. Therap.* **24**: 1, 1924.

infections are as relatively frequent in the milder types (I and IV) as in the severe types (II and III)

Twenty-four per cent of the cases of pneumococcic pneumonia showed pneumococci in the blood. The incidence of bacteremia is higher in the severe types (II and III) than in the mild types (I and IV). Type II is essentially the pneumococcus of bacteremia, yielding positive blood cultures in 39.7 per cent of the cases.

No striking differences in the clinical course could be demonstrated as characteristic of the various types of pneumococci. The average duration of the disease for the various types ranged from 8.6 to 9.1 days, type III running the longest course. Type III infections also run the longest course in monkeys.

A study of the mode of termination in the cases of pneumococcic pneumonia in which the patients recovered showed that 49.6 per cent terminated by crisis. Crisis was most frequent in type I infections, 56.6 per cent, type II, 50 per cent, type III, 39.3 per cent, type IV, 45.5 per cent.

The death rates for the various types (without specific treatment) were as follows: type I, 20.7 per cent, type II, 42 per cent, type III, 41.6 per cent, type IV, 29.2 per cent. Types I and IV are the milder forms, types II and III are the severe forms, of pneumococcic pneumonia.

A study of the death rate in relation to age shows a steadily increasing death rate for each decade. In patients under 20, the death rate for all types was 11.1 per cent, in those over 60, the death rate was 52.7 per cent. Age is probably the most important single factor in determining the death rate in pneumonia. Pneumococcus type I pneumonia has a low death rate, presumably because it is the pneumonia of young people. Pneumococcus type 3 pneumonia has a high death rate, chiefly because of its prevalence in elderly people. In patients under 30, type III pneumonia is not a severe infection.

The relation of bacteremia to death rate was striking in all four types. Among 240 patients whose blood remained sterile, the death rate was only 18.7 per cent, among eighty-nine patients whose blood cultures were positive, the death rate was 83.1 per cent.

The association of some systemic disease with pneumonia increases the death rate. Among patients free from systemic disease, the death rate was 23.4 per cent, among those with systemic disease, the death rate was 46.4 per cent.

In all four types of pneumonia the death rate was definitely related to the number of lobes involved, for single lobe infections it was 20.9 per cent, two lobes, 36.3 per cent, three lobes, 40.8 per cent, and four lobes, 65.5 per cent.

Some form of pneumococcic complication occurred in 12.1 per cent of type I cases. The incidence of pneumococcic complications was almost twice as high for type I infections as for the other three types.

Empyema was the commonest complication, occurring in 5.1 per cent of all cases. The incidence of empyema was considerably higher in type I infections than in any of the other types. Empyema is a much more serious complication when it develops during the active stage of pneumonia than when it occurs after the crisis.

THE CORONARY CIRCULATION *

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Experimental ligation of the coronary arteries¹ and observations on man following the occlusion of these vessels² have demonstrated that the heart is extremely sensitive to a reduction in its blood supply. It would seem that a knowledge of the factors concerned in the regulation of the coronary circulation is important for a better understanding of impaired cardiac function. It is possible that a further study of this subject may furnish an explanation for the cause of cardiac failure in certain instances which are at present obscure and may perhaps suggest a more satisfactory means of treatment. The present report is concerned with studies of certain features of the coronary circulation in which the author has been interested during the last three years.

INFLUENCE OF THE VAGI AND SYMPATHETIC NERVES ON THE CORONARY ARTERIES

The action of the vagi and sympathetic nerves on the coronary arteries has been more extensively investigated perhaps than any other physiologic aspect of the coronary circulation. It has been approached through the study of short sections of the coronary arteries suspended in Ringer's solution and through observation on the isolated and the intact heart and heart-lung preparation.

The studies on isolated sections of the coronary arteries have been concerned chiefly with observations on the effect of epinephrine because of the action that this drug is said to have on the sympathetic nerve.³ By this method epinephrine has repeatedly produced a dilatation of strips of coronary arteries from the sheep, goat, ox, calf and rabbit.

* From the Department of Internal Medicine, State University of Iowa.

* Read before the Portland Academy of Medicine, Portland, Oregon, Oct 13, 1926.

1 Miller and Mathews. Effect on the Heart of Experimental Obstruction of the Left Coronary Artery, *Arch Int Med* **3** 476 (June) 1909. Smith, F M. The Ligation of Coronary Arteries with Electrocardiographic Study, *ibid* **22** 8 (July) 1918.

2 Herrick, J B. Clinical Features of Sudden Obstruction of the Coronary Arteries, *J A M A* **59** 2015 (Dec 7) 1912, Thrombosis of Coronary Arteries, *ibid* **72** 387 (Feb 8) 1919.

3 Lagendorff. *Zentralbl f Physiol* **21** 551, 1907. Cow. *J Physiol* **42** 125, 1911. Eppinger and Hess. *Ztschr f exper Path u Therap* **5** 622, 1909. Barbour. *J Exper Med* **15** 404, 1912. Park. *ibid* **17** 532, 1912. Ishihara. *Fuknoka-Ihwadagaku-Zasshi* **14** 3, 1921.

Barbour,⁴ however, who used human coronary arteries removed at autopsy while the body was still warm, observed a constriction, but in a similar series of experiments, he noted a dilatation when the coronary arteries of the calf, sheep and pig were employed. Cow⁵ reported that the strips taken from different sections of the same artery varied in their response to epinephrine. While this method of investigation has yielded certain important information, it is subject to criticism because of the obviously abnormal state under which these vessels were studied. Furthermore, since the smaller arteries and the capillaries, in many instances, are known to react in a different manner from the larger vessels,⁶ observations made on the isolated ring preparations cannot be applied to the whole coronary system without reservations.

In the studies on the isolated heart the perfusion fluid was introduced through a cannula inserted into the aorta or into the coronary arteries. Wiggers⁷ has pointed out a possible source of error in determining the rate of coronary flow by perfusion of the heart through a cannula inserted into the aorta because of the possible imperfect closure of the aortic valves allowing a leakage of fluid into the left ventricle. He eliminated this source of error by introducing the cannulas directly into the coronary arteries.

My co-workers and I⁸ have recently investigated the question of the leakage of the aortic valves. In some experiments the inferior and superior vena cava were ligated and a cannula introduced into the pulmonary artery. The return of the perfusion fluid to the right side of the heart was thus separated from any that might leak past the aortic valves or return directly to the left ventricle from the coronary circulation. The same feature was further studied by the ligation of the pulmonary veins and by the insertion of a cannula into the tip of the left auricle. In both instances the amount of perfusion fluid which escaped from the left ventricle was negligible.

The rate of coronary flow in the perfused heart has usually been determined by measuring the fluid which escapes from the right auricle. In a series of experiments performed by my co-workers and me, the perfusion fluid escaping from the right auricle has been directed by a funnel into a tipping bucket, the emptying of which is automatically registered on a kymograph. Brodie and Cullis⁹ devised an ingenious plethysmograph by means of which a constant record of the coronary

4 Barbour (footnote 3, fourth reference)

5 Cow (footnote 3, second reference)

6 Krogh, *J Physiol* **53** 399, 1919-1920, *ibid* **55** 412, 1921, *The Anatomy and Physiology of Capillaries*, Yale University, New Haven, 1922

7 Wiggers *Am J Physiol* **24** 391, 1909

8 Smith, Miller and Graber *J Clin Investigation* **2** 157, 1925

9 Brodie and Cullis *J Physiol* **43** 313, 1911-1912

outflow was obtained Sassa,¹⁰ and Drury and Sumbal¹¹ have employed the method introduced by Atzler and Frank¹² for measuring the coronary inflow. The latter method is perhaps the most delicate means of registration, but is dependent on a closed system which somewhat restricts its field of application.

In the intact heart the rate of coronary flow has been estimated by measuring the blood permitted to escape through a cut in a coronary vein.⁷ More recently the Morowitz and Zahn cannula,¹³ which is introduced into the coronary sinus, has been employed.¹⁴ This cannula has also been used in the heart-lung preparation.¹⁵ It affords an accurate means of studying the rate of coronary flow. While not all the blood returns to the right side of the heart through the coronary sinus, this amount has been found by Starling to represent a fairly constant proportion of the total coronary flow under varying conditions.

Epinephrine has likewise been employed in the study of the coronary circulation of the isolated¹⁶ and intact heart¹⁷ and in the heart-lung preparation¹⁸ by observing the effect of the drug on the rate of coronary flow. In most instances the rate of flow was increased. The dose of the drug employed was usually sufficient to produce a striking accelerating action on the heart. Brodie and Cullis⁹ avoided the marked stimulating effects of epinephrine by reducing the size of the dose. In those instances in which minute quantities were employed, a decrease in the rate of perfusion was observed. As the size of the dose was increased, causing the stimulating action to become more marked, the decrease in the rate of coronary flow was replaced by augmentation.

Recently Drury and Smith,¹⁹ by means of the microscope, studied the effects of epinephrine applied locally to the coronary arteries of the tortoise. In all instances the vessels under observation were constricted. Sometimes the lumen was entirely obliterated. After the vessels were constricted by epinephrine, they were dilated to their

10 Sassa Arch f d ges Physiol **198** 543, 1923

11 Drury and Sumbal Heart **10** 267, 1924

12 Atzler and Frank Arch f d ges Physiol **181** 144, 1920

13 Morowitz and Zahn Zentralbl f Physiol **26** 465, 1912, Deutsches Arch f klin Med **116** 364, 1914

14 Sassa (footnote 10) Smith, Miller and Graber Relative Importance of Systolic and Diastolic Blood Pressure in Maintaining Coronary Circulation, Arch Int Med **38** 109 (July) 1926

15 Markwalder and Starling J Physiol **47** 275, 1913-1914 Nakagawa J Physiol **56** 340, 1922 Anrep Physiol Rev **6** 596, 1926

16 Barbour and Prince J Exper Med **21** 330, 1915 Bond ibid **12** 575, 1910 Schafer Zentralbl f Physiol **19** 218, 1905-1906 Wiggers (footnote 7)

17 Meyer Arch f Anat u Physiol 1912, p 223 Morowitz and Zahn (footnote 13) Wiggers (footnote 7)

18 Markwalder and Starling (footnote 15, first reference)

19 Drury and Smith Heart **11** 71, 1924

original size by faradic stimulation of the vagus. This dilating action of the vagus was readily eliminated by atropine. Drury and Sumbal¹¹ later noted a striking decrease in the rate of the coronary flow in the heart of a tortoise after the introduction of epinephrine into the perfusion fluid. In the same series of experiments similar results were obtained by the stimulation of the sympathetic nerves. In further observations on the coronary arteries of the tortoise, Sumbal²⁰ studied the effects of acetylcholine by direct application and perfusion methods. When the drug was applied locally to the coronary artery, a dilatation was noted, and when it was introduced into the perfusion fluid, an increase in the rate of coronary flow followed.

I²¹ have more recently studied the effect of epinephrine and acetylcholine on the coronary flow in the perfused heart of the rabbit. Epinephrine in dilutions of approximately 1:200,000,000 was employed to avoid the complicating effects produced by the extreme cardiac stimulation resulting from the higher concentrations ordinarily used. Epinephrine in this dilution produced a decrease in the rate of the coronary flow varying from 12 to 22 per cent. The diminished perfusion rate began immediately after the introduction of the drug and persisted up to the point of greatest cardiac stimulation. At this point the coronary flow was usually slightly augmented for a short time. Even with these minute doses of epinephrine there was a distinct stimulating effect on the heart as indicated by the acceleration in rate and increase in the amplitude of contraction. These results demonstrate that epinephrine constricts the coronary arteries of the rabbit when the dose employed is sufficiently small to avoid the extreme cardiac stimulation. When larger concentrations were used, the decrease in the rate of coronary flow was replaced by an augmentation. It is believed that the increase in the rate of coronary flow heretofore reported may be attributed to the extreme stimulating action on the heart by the dose employed.

Acetylcholine is generally regarded as having an inhibitory action on the heart comparable to that produced by stimulation of the vagus.²² In the aforementioned investigation acetylcholine was introduced into the coronary arteries in dilutions varying from 1:100,000 to 1:200,000. The drug in these concentrations greatly reduced the heart rate, and in some instances produced cardiac standstill. Coincident with the reduction in the rate, the amplitude of contraction was diminished. With the onset of these changes, the perfusion rate was greatly augmented. The introduction of atropine into the perfusion fluid in a concentration of

²⁰ Sumbal. *Heart* **11** 285, 1924.

²¹ Smith, Miller and Graber. *Am J Physiol* **77** 1, 1926.

²² Hunt and DeM. Taveau. *Brit M J* **2** 1788, 1906. Dale. *J Pharmacol & Exper Therap* **6** 147, 1914. Hunt. *Am J Physiol* **45** 197, 1918.

1 20,000 prevented or eliminated these effects. The results were thus similar to those observed by others in the study of the action of acetylcholine on the coronary artery of the tortoise²⁰ and on other arteries in the mammal²³.

The results of stimulation of the sympathetic and of the vagus nerves of the mammal have varied in the hands of different investigators. Morawitz and Zahn¹³ observed an increase in the rate of coronary flow during sympathetic stimulation. In these experiments neither the cardiac rate nor the blood pressure was controlled. Wiggers⁷ reported a decreased flow from a wounded coronary vein during the stimulation of the vagosympathetic nerves of the dog after atropinization. Nakagawa²⁴ noted no change in the rate of coronary flow in the heart-lung preparation during vagal stimulation. Sassa¹⁰ studied the coronary flow by cannulizing the coronary arteries in the intact and isolated heart of the cat and measured the rate of inflow by the Atzler and Frank method. A decrease in the rate of flow was usually recorded at the beginning of sympathetic stimulation even with increased cardiac rate, whereas on vagal stimulation there was an initial increase in the rate of inflow associated with a reduction in the cardiac rate.

The question as to whether the vagi and sympathetic nerves provide the coronary arteries with a vasomotor mechanism has been difficult to answer. It is not surprising that the results from the use of epinephrine and electrical stimulation of the nerves have varied because of the difficulty in controlling of the various factors which influence the coronary circulation. The contraction of the heart opposes either a dilatation or a constriction of the coronary arteries. The opposition from this factor is conceived to be great in the mammalian heart because of the rapid rate of contraction. This feature is well illustrated by the action of epinephrine on the isolated or intact heart when the dose is sufficient to produce a marked stimulating effect. It is perhaps reduced to the minimum in the slowly beating heart of the tortoise. Even here it was difficult to obtain the constricting effect of epinephrine on the surface vessels after the cardiac rate was accelerated by the stimulating effect of the drug¹⁰. Furthermore, the blood pressure is perhaps the greatest factor in maintaining the coronary circulation. This has not always been controlled. Then, too, the vagi and the sympathetic nerves are apt not to be clearly separated in the mammal, particularly in the dog, in which the main trunk of the vagus is said to contain sympathetic fibers. The possibility of stimulating both nerves when intending to stimulate only one cannot be entirely disregarded. At present it would seem that there is no doubt regarding the action of the vagi and sympathetic nerves on the coronary artery of the tortoise. The

23 Hunt (footnote 22, third reference)

24 Nakagawa (footnote 15, second reference)

evidence that these nerves may provide the coronary arteries of the mammal with a similar vasomotor mechanism is suggestive but not conclusive

THE INFLUENCE OF BLOOD PRESSURE

The susceptibility of the heart to changes in the aortic pressure was early recognized in perfusion experiments. Heilitzka²⁵ observed that the perfused heart of the rabbit ceased to beat when the pressure of the perfusion fluid was reduced below from 13 to 18 mm of mercury. If, however, the pressure was gradually increased, the cardiac contractions appeared in periodic groups. After further increase in pressure, the action of the heart became more regular with alternating strong and weak beats which were later replaced by contractions of equal strength. Langendorff²⁶ and Porter²⁷ noted that an increase in perfusion pressure greatly augmented the rate of coronary flow. The influence of blood pressure on the coronary flow was perhaps best appreciated following the observations of Markwalder and Starling¹⁶. In some instances they obtained 100 per cent increase in the rate of coronary flow by elevating the blood pressure from 80 to 100 mm of mercury. Morawitz and Zahn¹³ and De Barenne²⁸ have since observed a similar dependence of the coronary flow on the arterial pressure.

Recently I²⁹ studied the relative importance of the systolic and diastolic pressure in maintaining the coronary circulation. Dogs were employed in this series of experiments. The blood pressure was recorded on the kymograph by a Straub membrane manometer. This instrument was employed in order to obtain a more accurate record of the systolic and diastolic pressures. The rate of coronary flow was determined by means of the Morawitz-Zahn cannula. The blood from the coronary sinus was maintained at a constant temperature and reintroduced into the femoral vein. Changes in the blood pressure were produced by constricting the thoracic aorta with an adjustable clamp and by the experimental production of arteriovenous aneurysm and aortic regurgitation.

In those experiments in which the thoracic aorta was constricted by an adjustable clamp, it was possible, within certain limits, to increase the diastolic pressure without altering the systolic pressure. In each instance there was a striking increase in the rate of coronary flow associated with the elevation of the diastolic pressure, even in those experiments in which the systolic pressure was slightly reduced.

25 Heilitzka. *Tierstadt Physiologie des Kreislaufes*, Berlin, 1921, vol. 1, p. 319.

26 Langendorff. *Arch f d ges Physiol* **78** 423, 1899.

27 Porter. *Am J Physiol* **1** 141, 1898.

28 De Barenne. *Arch f d ges Physiol* **177** 217, 1919.

29 Smith, Miller and Graber (footnote 14, second reference).

When the arteriovenous aneurysm was employed, the diastolic pressure was reduced and the systolic increased. In these experiments there was a definite decrease in the rate of coronary flow in spite of the increase in the systolic pressure. In the experiments in which an aortic regurgitation was produced by puncturing the aortic valves, the results were similar to those of the arteriovenous aneurysm. The systolic pressure was increased, the diastolic decreased, and there were corresponding changes in the coronary flow. The alterations in the blood pressure and the changes in the coronary flow varied with the extent to which the aortic valves were damaged. In one typical experiment during the control period the systolic pressure was 100 and the diastolic 50. The rate of flow from the coronary sinus was 240 cc a minute. Following the puncture of one valve the systolic pressure was increased to 120 and the diastolic fell to 30. The flow from the coronary sinus was reduced to 195 cc a minute. Later the same valve cusp was torn loose from its base. Following this procedure the systolic pressure at once increased to 150 and the diastolic fell to 15. The flow from the coronary sinus was further reduced to 150 cc a minute.

The results of this series of experiments show that the rate of coronary flow is greatly altered by a change in the diastolic pressure even in the presence of changes in the systolic pressure in the opposite direction. In one instance in which there was a reduction of only 5 mm of mercury in the diastolic pressure associated with an increase of 10 in the systolic pressure, there was a decrease in the flow of the blood from the coronary sinus from 277 to 250 cc a minute. Similarly in those experiments in which there was a corresponding elevation of the diastolic pressure, even though the systolic pressure remained constant or was even slightly reduced, there was a comparable increase in the rate of coronary flow. It would seem from these results that the maintenance of an efficient coronary circulation is fundamentally dependent on the height of the diastolic pressure. While the systolic blood pressure no doubt influences the coronary flow, it is subordinate to that of the diastolic pressure.

On the basis of these observations it is suggested that the decreased coronary flow associated with the diminished diastolic pressure in aortic regurgitation and arteriovenous aneurysm is probably a significant factor in the development of the cardiac hypertrophy and later cardiac failure.

INFLUENCE OF THE CARDIAC RATE

Porter²⁷ observed a decrease in the rate of coronary flow in the perfused heart of the cat when the cardiac rate was slowed by vagal stimulation. He concluded that the volume of blood passing through the coronary vessels was influenced by the heart rate. The effect of variations in the cardiac rate on the coronary circulation has since been

studied by Morawitz and Zahn,¹³ Nakagawa,²¹ Sassa,¹⁰ Miyaka,³⁰ Anrep and Segall³¹ and Hammouda and Kinoshita³² Nakagawa employing the heart-lung preparation and Sassa in studies on the isolated heart produced changes in the heart rate by altering the temperature of the blood or perfusion fluid. In both series of experiments the reduction and the acceleration in the cardiac rate, induced respectively by cooling and heating of the blood or perfusion fluid, produced within certain limits a corresponding increase and decrease in the rate of coronary flow. Both of these investigators appreciated that the changes in the coronary flow induced in this manner could not be entirely attributed to changes in the cardiac rate, they therefore resorted to other means of changing the rate. Nakagawa, in his further experiments, accelerated the heart rate by induced shocks to the sinus node and slowed the heart by vagal stimulation. In this study, no appreciable change was noted in the rate of coronary flow. In his subsequent studies, Sassa, induced changes in the cardiac rate by cooling and warming the sinus node by means of a water thermode. He observed a decrease in the coronary flow when the cardiac rate was reduced. In those instances, however, in which heat was applied to the sinus node associated with an acceleration in cardiac rate there was little increase in coronary flow.

Observations on the effects of changes in the cardiac rate produced by warming and cooling the sinus node have since been made by Miyaka, and no alteration in the coronary flow has been observed. Anrep and Segall, working with the heart-lung preparation, did not note any change in the volume of the coronary flow by driving the heart at varying rates from 60 to 200 a minute. These observers cite the work of Hammouda and Kinoshita on the isolated heart as confirming their results.

My co-workers and I³³ have recently investigated the influence of cardiac rate on coronary flow. The subject was approached by studies on the isolated and on the intact heart. In the former the heart of the rabbit was driven at different rates by means of rhythmical induced shock. In every instance an increase in heart rate was associated with an augmentation of the coronary flow. In general the increase in coronary flow seemed to depend on the initial cardiac rate and the extent to which the heart was accelerated. The greatest increase in the rate of coronary circulation was observed in those instances in which the initial cardiac rate was about 120 and the acceleration more than 50 beats a minute. A further increase in the cardiac rate above 200 a minute usually did not produce significant changes in the coronary flow. Fur-

30 Miyaka, quoted by Anrep (footnote 15, third reference)

31 Anrep (footnote 15, third reference)

32 Hammouda and Kinoshita, quoted by Anrep (footnote 15, third reference)

33 Smith, Miller and Graber. Unpublished work

therefore, in those experiments in which the initial heart rate was above 160 a minute, further acceleration was not associated with changes in the coronary flow comparable to that produced in a heart with a lower initial rate.

Further studies were made on the intact heart of the dog in which changes in the cardiac rate were produced by heating and cooling the sinus node and by vagal stimulation. In all instances a constant blood pressure was maintained. By means of the application of heat and cold to the sinus node, it was possible to produce changes in the cardiac rate ranging from 30 to 60 beats a minute. This decrease and increase in heart rate, respectively, was associated with a sudden reduction and augmentation of the coronary flow. In those experiments in which the cardiac rate was decreased by vagal stimulation, the reduction in the rate of coronary circulation was striking.

It is concluded from these results that reduction and acceleration of the cardiac rates within certain limits are associated with definite changes in the rate of coronary flow. The most striking alterations in the coronary circulation were observed during the changes from the slow beat induced by vagal stimulation to the accelerated rate produced by warming the sinus node.

THE INFLUENCE OF CARDIAC IRREGULARITIES

The coronary circulation has been studied during ventricular fibrillation. Anrep, in his recent review,³¹ mentions an investigation in which he, with Downing, Cruickshank and Subba Rao studied the time relations between the changes in the coronary outflow and inflow and the different phases of the cardiac cycle in the heart-lung preparation. In this work observations were made on the influence of heart block, premature contraction and auricular and ventricular fibrillation. No definite statement, however, was made concerning the influence of these various types of abnormal cardiac mechanism on the rate of coronary flow, and a detailed report of these experiments is not available. To my knowledge, there has been no other observation concerning the influence of the clinical types of cardiac irregularities on the coronary circulation.

This subject is being investigated on the intact heart of the dog and will be discussed more in detail in a future report. So far, premature contraction induced by electrical stimulation of the auricles and ventricles has not produced any significant change in the rate of coronary flow. The effects of auricular fibrillation produced by faradic stimulation of the auricles have varied. In most instances there has been a definite increase in the rate of coronary flow. In one experiment, however, in which the auricular fibrillation appeared spontaneously and lasted for several minutes, there was practically no change in the rate of coronary flow after the establishment of a normal cardiac mechanism. In another

experiment, in which the faradic stimulation of the auricles was followed on several occasions by the onset of a rapid and seemingly regular cardiac action, there was no significant change in the rate of flow from the coronary sinus

A slow cardiac rate comparable to that accompanying complete heart block was produced by vagal stimulation. In each of these experiments there was a striking reduction in the rate of coronary flow

THE INFLUENCE OF CAFFEINE, THEOBROMINE AND THEOPHYLLINE

Caffeine, theobromine and theophylline are invariably mentioned in the discussion of the treatment of patients with cardiac failure. One explanation of their beneficial effect has been sought through their possible action on the coronary arteries. The results of the investigation of the action of these drugs on the coronary arteries have varied considerably with the different observers. Hedbom³⁴ obtained an increase in the rate of coronary flow in the perfused heart with caffeine in concentration of 1:20,000. Loeb,³⁵ on the other hand, observed little increase in the coronary output following the administration of caffeine, whereas theobromine greatly augmented the rate of perfusion. Heathcot³⁶ studied the action of caffeine, theobromine and theophylline in concentration varying from 1:2,000 to 1:40,000. He obtained a marked increase in rate of coronary flow with the higher concentration. When, however, these drugs were employed in dilutions of 1:20,000 and 1:40,000, caffeine and theobromine produced little if any change, and theophylline produced from 20 to 30 per cent increase. Sakai and Saneyoshi³⁷ investigated the effect of caffeine sodiobenzoate and theobromine sodiosalicylate on the coronary flow of the intact heart of the cat, employing the Morowitz-Zahn cannula in their experiments. They concluded that the slight increase in the coronary output which they observed following the injection of caffeine sodiobenzoate could satisfactorily be explained on the basis of the elevation in blood pressure. Small doses of theobromine sodiosalicylate produced slight increase in the coronary flow, whereas when large doses were introduced, there was a drop in the blood pressure associated with a marked augmentation of the flow through the coronary arteries. Guggenheimer and Sassa³⁸ studied the action of caffeine, theophylline and euphyllin on the coronary arteries of the isolated heart of the cat. Caffeine in dilutions of 1:25,000 increased the rate of coronary flow 41 per cent. Theophylline and euphyllin in similar concentrations produced a 40 and 80 per cent

34 Hedbom. *Skandin Arch f Physiol* 9:1, 1899

35 Loeb. *Arch f exper Path u Pharmacol* 51:64, 1903-1904

36 Heathcot. *J Pharmacol & Exper Therap* 16:327, 1920

37 Sakai and Saneyoshi. *Arch f exper Path u Pharmacol* 78:331, 1914-1915

38 Guggenheimer and Sassa. *Klin Wchnschr* 2:1451, 1923

increase, respectively. These investigators attributed the change in the rate of the flow of the perfusion fluid after caffeine and theophylline to the acceleration of the cardiac rate, and pointed out that euphyllin did not elevate the heart rate more than 10 per cent. The latter preparation was thus recommended therapeutically in coronary disease because of its marked dilating action.

We have compared the action of euphyllin with that of caffeine sodiobenzoate, theobromine sodiosalicylate and theophylline in experiments on the isolated heart of the rabbit in which the cardiac rate was controlled. Caffeine sodiobenzoate in concentrations of 1:25,000 solution had little if any effect on the cardiac rate, amplitude of contraction and coronary flow. Theobromine sodiosalicylate in dilutions of 1:25,000 in most instances produced no change or even decreased the coronary flow. When the concentration of 1:50,000 was used, the rate of flow was slightly accelerated. Theobromine sodiosalicylate in either of these concentrations apparently had no effect on the cardiac rate. In some instances the amplitude of contraction was diminished and associated with some increase in tone.

Theophylline in concentrations of 1:25,000 and 1:50,000 increased the rate of coronary flow from 20 to 45 per cent. The acceleration of the cardiac rate was not a prominent feature. The greatest increase in coronary flow was produced by the drug when there was no change in the cardiac rate.

Euphyllin in concentrations of 1:25,000 and 1:50,000 increased the rate of perfusion from 40 to 90 per cent. It had a somewhat greater tendency to accelerate the cardiac rate than did theophylline. With both drugs, however, the increase in coronary output was independent of the accelerating action on the heart, as was indicated by experiments in which uniform cardiac rate was maintained by rhythmical stimulation.

The variations in the results obtained in the investigations of the action of caffeine, theobromine and theophylline on the coronary arteries have apparently been due to the difference in the concentration of the drug employed. The concentrations employed in our experiments were similar to those used by Guggenheimer and Sassa and estimated to approximate the therapeutic dose in man. In those instances in which higher concentrations were employed, particularly as 1:2,000, the results obtained were probably due to the toxic action of the drug on the heart.

BASAL METABOLISM IN VITAMIN B STARVATION^{*}

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The basal metabolism in vitamin B starvation has been much discussed by various workers in recent years. The earliest article now available to us is that of Caspari and Moszkowski.¹ After practical experience during research in New Guinea, Moszkowski concluded that the so-called beriberi of man is a disease of metabolism essentially due to the ingestion of polished rice, a view which was contradicted by other workers. To verify this opinion, Moszkowski offered to make experiments on himself. He was kept under observation by Caspari and others. About a month after the beginning of the rice diet, clinical symptoms began to appear, which eventually became significant. The chief symptoms were general wandering neuralgia, tenderness of the muscles and skin, especially of the calf muscles, Lasegue's symptom, paresthesia and numbness of the hands and feet, weakness and somnolence, a sense of restriction in the chest, lability of the pulse, edema of the feet, painful effusion of the tendon sheaths especially of the hands and ankles, and looseness of the knees. The heart was slightly enlarged to the right and markedly to the left, extending 2 cm beyond the nipple line, this can be accounted for in part by the marked elevation of the diaphragm. The sounds were dull everywhere, the first sound at the apex being distinctly impure, the second pulmonic sound was accentuated. The motor nerve did not show any direct reaction of degeneration, the knee and achilles reflexes were active.

The clinical symptoms other than those of the heart were similar to those of the enterotoxic polyneuritis of von Noorden, especially as during the course of the disease there was a severe membranous enteritis, which is the chief clinical symptom in von Noorden's disease. A consideration of all the symptoms, especially those of the heart, and their prompt amelioration by the administration of the extract of rice bran, led the observers to conclude that this was a case of beriberi.

In the course of the research, Caspari and his associates found that the consumption of oxygen and the body weight diminished steadily. This was true, however, only during the first period of the research.

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¹ Caspari, W., and Moszkowski, M. Weiteres zur Beriberi-Frage, *Berlin Wehnschr* **50** 1515, 1913.

Later a distinct increase was observed in the consumption of oxygen. An increase in the basal metabolism is known to occur only as the result of some irritation or intoxication. To the first mechanism belongs also the product of internal secretion, such as that of the sexual and thyroid glands. Research work on respiration has shown that a toxic or irritating substance may exist in an organism. On the other hand, when experimenters fed pigeons with eggs of the domestic fowl, salts and grape sugar for more than a month, the animals showed an increase in weight and were healthy. They then added a sufficient amount of polished rice to this diet, and found that within varying periods polyneuritis developed. They concluded from the foregoing experiments that the development of beriberi does not depend on deficiency in nutrition but on the presence of a toxic substance, that is, on an intoxication.

Ramoino² found that by feeding pigeons exclusively with polished rice a rapid decrease of the respiratory quotient occurred, but that it soon became normal when an extract prepared from rice bran was given. He attributed this phenomenon to the lack of vitamin which has a catalytic action, and consequently to insufficient oxidation of the nutritive substances. The accumulation of the intermediate catabolic products has an intoxicating effect on the tissues and causes the characteristic symptoms. A review of Ramoino's protocols shows that the body weight and consumption of oxygen of animals fed on polished rice were simultaneously reduced. The decrease in consumption of oxygen was in some cases nearly parallel with the decrease in body weight, while in others it was more marked.

Abderhalden³ and his co-workers made an extraordinary series of observations on the gas exchange of the entire animal as well as of isolated cells and tissues of pigeons suffering from alimentary dystrophy, and found that the gas exchange in both was markedly diminished. The foodstuffs which prevent the appearance of the well known symptoms after a diet consisting exclusively of polished rice, or which cause them to disappear, also cause cell respiration to be increased. For example, in pigeons that were fed exclusively on polished rice and showed lowered temperature and decreased gas exchange, the gas exchange increased promptly and the temperature became normal when a small amount of foodstuffs prepared from yeast or rice bran was

² Ramoino, P. Contributo allo studio delle alimentazioni incomplete. *Pathologica* **7** 101, 1915.

³ Abderhalden, E., and Schmidt, L. Weitere Beiträge zur Kenntnis von organischen Nahrungsstoffen mit spezifischer Wirkung, III. Mittel, *Pflüger's Arch f d ges Physiol* **185** 141, 1920. Abderhalden, E. IV. Mittel, *ibid* **187** 80, 1921, V. Mittel, *ibid* **188** 60, 1921. Abderhalden, E., and Wertheimer, E. VII. Mittel, *ibid* **191** 258, 1921. Abderhalden, E. VIII. Mittel, *ibid* **191** 278, 1921, IX. Mittel, *ibid* **192** 163, 1921. Abderhalden, E., and Wertheimer, E. X. Mittel, *ibid* **192** 174, 1921, XIII. Mittel, *ibid* **194** 647, 1922, XVII. Mittel, *ibid* **195** 460, 1922.

administered. The cells and tissues of pigeons which suffered from alimentary dystrophy, and which showed a decrease in respiration, showed an immediate increase in the consumption of oxygen when the aforementioned foodstuffs were added to the diet. From all these observations, it was concluded that on a diet consisting exclusively of polished rice, the cell respiration becomes poor, and oxidation is restricted. Respiration also becomes longer and deeper in pigeons fed on rice. Further research also confirmed the observation that pigeons fed on rice show an increased sensibility to deficiency in oxygen and increase in carbon dioxide.

Hess and Messerle⁴ made investigations concerning the respiratory power of various tissues of pigeons diseased from feeding on rice, and compared it with that of healthy pigeons. The diseased pigeons showed a marked insufficiency of respiration in various tissues, especially in the brain.

Anderson and Kulp⁵ found that in poultry fed exclusively on polished rice there was a lowering of the basal metabolism and a decrease in the consumption of food with loss in weight, and that in from thirty-eight to forty-four days symptoms of paralysis appeared. They observed that the heat production of chickens, when calculated on the basis of kilograms of weight, decreased from 3 calories during usual nourishment to about 2.25 calories per kilogram per hour during vitamin starvation and polyneuritis. A single administration of yeast extract not only relieved the symptoms of polyneuritis, but also started an extremely active metabolism. During the first two or three weeks after recovery, the consumption of food was small, and there was little gain in weight. The heat production of the emaciated organism, however, was equal to that of the well nourished animal. These authors found almost no difference in the value of the respiratory quotient during vitamin starvation and during normal basal metabolism, this agrees with the results of Janson and Mangkoewinoto, but which differs from those reported by Ramoino.

Kinoshita⁶ found that giving pigeons food deficient in vitamin B caused a marked diminution of the respiratory quotient during the later period of incubation and especially after the appearance of polyneuritis. The consumption of oxygen increased, however, especially during the last stages of the disease as compared with that of the period of incubation.

4 Hess, W. R. Die Rolle der Vitamine im Zellmechanismus, *Ztschr. f. phys. Chem.* **117** 284, 1921. Hess, W. R., and Messerle, N. Untersuchungen über die Gewebeatmung bei Avitaminose, *ibid.* **119** 176, 1922.

5 Anderson, R. J., and Kulp, W. L. A Study of the Metabolism and Respiratory Exchange in Poultry During Vitamin Starvation and Polyneuritis, *J. Biol. Chem.* **52** 69, 1922.

6 Kinoshita, R. Ueber den Gaswechsel bei der Reiskrankheit des Geflügers, *Tr. Japanese Path. Soc.* **12** 186, 1922.

From this observation he considered that the ingredients which are oxidized as the source of energy in the body of pigeons fed on rice must be other than carbohydrate, although this is administered in sufficient amount. This fact proves the opinion of Ogata and his co-workers that the vital point of the rice disease is a disturbance of the metabolism of carbohydrate as the result of vitamin B deficiency.

We⁷ made an investigation in persons with mild cases of beriberi in which the basal metabolism was normal or nearly normal, as well as in healthy men, to determine whether any change occurs in the basal metabolism or in the variation in the respiratory exchange during vitamin B starvation. The main part of the diet consisted of well polished and thoroughly washed rice, and the additional foods were free from vitamins but contained enough protein, fat and salts. The basal metabolism decreased during vitamin B starvation and rapidly became normal after the administration of vitamin B preparations. In vitamin B starvation we often found loss of appetite and decrease in consumption of food, but the lowering in the basal metabolism occurred before there was a change in appetite, consumption of food or body weight. On account of the respiratory quotient, we could not find any definite change in metabolism during the course of vitamin B starvation, although it seemed somewhat likely to become lower.

Groebbels⁸ determined the consumption of oxygen in white mice fed with polished rice. He found that the increase in the consumption of oxygen and body weight during the first period of vitamin starvation was accompanied by a decrease in both during the following period. He called these two periods the avitaminosis period and the starvation period. He attributed the former to insufficiency of vitamin and the latter, not directly to avitaminosis, but to the secondary disturbance of metabolism of protein and salts following vitamin starvation.

Knipping and Kowitz⁹ made an experiment on human subjects suffering from scurvy by administering food autoclaved three hours at 130 C. They found a marked increase in the basal metabolism when the food contained vitamins. After the administration of vitamin preparations, a diminution of metabolism was observed in all cases.

7 Okada, S., Sakurai, E., Ibuki, T., and Kabeshima, H. On the Basal Metabolism in Vitamin B Starvation and in Beriberi, *Ikai Jiho* no 1479 (Nov. 4) 1922, *Japan M. World* **3** 102 (May 15) 1923.

8 Groebbels, F. Studien über das Vitaminproblem. I. Mittel, Untersuchungen über das Gasstoffwechsel avitaminotisch ernährter weisser Mäuse, *Ztschr. f. phys. Chem.* **122** 104, 1922, *Klin. Wchnschr.* 1548, 1922, II. Mittel, Untersuchungen über den Einfluss der Vitaminzufuhr und des Hungerns auf Gasstoffwechsel, Gewicht und Lebensdauer vitaminfrei ernährter weisser Mäuse, *Ztschr. f. phys. Chem.* **131** 214, 1923, III. Mittel, Weitere Untersuchungen über den Einfluss der Vitaminzufuhr auf Gaswechsel, Gewicht und Lebensdauer vitaminfrei ernährter weisser Mäuse, *ibid.* **137** 14, 1924.

9 Knipping and Kowitz. Untersuchungen über die Avitaminose beim Menschen, *München med. Wchnschr.* **70** 46 (Jan. 12) 1923.

Contrary to the observations of previous workers, Magne and Simonnet¹⁰ found that in pigeons neither the respiratory quotient nor the consumption of oxygen changed as the result of vitamin starvation.

Bickel¹¹ and his co-workers made numerous experiments on animals to determine the metabolism in vitamin starvation. Bickel concluded from these investigations that the incubation period of avitaminosis, as he calls it, during which there may be an increase in body weight, is not long, and that two phenomena soon appear: a decrease in consumption of oxygen and the invasion of the blood by sugar and fat as a consequence of the evacuation of glycogen and fat, both being an expression of a powerful stuff mobilization. The decrease in consumption of oxygen and body weight is observed when sufficient calories of food are absorbed. Bickel finds the absorption of food even greater during prolonged vitamin starvation than during a normal period when there are no disturbances of the stomach and intestine. From these observed phenomena it is clear that the decreased consumption of oxygen is a primary symptom of avitaminosis, and that it has nothing to do with the disturbance of absorption in the intestinal tract, that is, with undernutrition or hunger. The oxidation of protein and fat has been proved to increase during vitamin starvation, and this with retardation of sugar catabolism causes a lowering of the respiratory quotient. The intake of oxygen and the elimination of carbon dioxide are diminished, and as the protein catabolism continues in an almost normal manner, so that increased consumption of oxygen is required because of the increased protein catabolism and also because of the intermediate metabolism, at least in the usual relation of avitaminosis, evidences of disturbance in the oxidation of fat are not perceivable, on the contrary, an increased and continuous fat catabolism occurs in the whole organism. Sugar catabolism must go on with decreased consumption of oxygen and consequent decrease in the elimination of carbon dioxide. Notwithstanding the increased protein and fat catabolism, the basal metabolism, measured by gas exchange, is distinctly diminished. This is the case in actual avitaminosis, in which food containing enough calories of protein, fat and carbohydrate is thoroughly absorbed. This is possible only when the oxidation of sugar, and, as a result, the production of carbon dioxide, are extraordinarily restricted, and necessitate an increase in the consumption of oxygen and protein and probably of fat, accompanied by an increase in the production of carbon dioxide through oxidation of sugar. As carbohydrate is also thoroughly absorbed, the dysoxidizable

10 Magne, H, and Simonnet, H. Sur les variations du quotient respiratoire chez le pigeon carence, *Bull. Soc. de chem. biol.* **4** 419, 1922.

11 Bickel, A. Das Wesen der Avitaminose. Nach experimenteller Untersuchung über die Abmagerungsform dieser Krankheit, *Biochem. Ztschr.* **146** 493, 1924, Weitere Untersuchungen über den Stoffwechsel bei der Avitaminose, *ibid.* **166** 251, 1925.

products thus must accumulate in the body or may be eliminated in the urine. Urimalysis showed that by avitaminosis the dysoxidizable carbon of the urine increases, and, notwithstanding the excretion of nitrogen, is at first unchanged, and later increased, and that the urine quotient—carbon/nitrogen—becomes higher. In the middle period of the disease, perhaps accompanied by the elimination of fat, the quotient is especially high, showing some decrease at a later stage, but it is always pathologically high. The increase of lactic acid in the urine during avitaminosis is slight and cannot explain the marked increase in the quotient.

Yanagi¹² determined the consumption of oxygen of rats and human subjects in vitamin starvation, in general, he found a significant decrease, with more or less fluctuation. When the animals were fed with diets containing some but not a sufficient amount of vitamins, the body weight increased during the first two or three weeks, followed by a decrease later. The consumption of oxygen, however, was diminished when the body weight still continued to increase, and became more significant and especially marked when paralysis developed. During the last period, it sometimes tended to increase again. After the administration of vitamin B preparations, the consumption of oxygen increased promptly with appetite and body weight if the paralysis was not too extreme.

Goh¹³ observed the gas exchange in pigeons during the course of relative insufficiency of vitamins. These pigeons showed symptoms of avitaminosis for from one hundred and thirty-one to two hundred and twenty-four days after the beginning of the special diet. The respiratory quotient gradually became lower during the period of incubation, about twenty days before polyneuritis appeared. During the period of polyneuritis it became especially low, in all cases being less than 0.7. The intake of oxygen, however, was unchanged or increased. The author concluded from this result that in avitaminosis the oxidation of carbohydrate is extremely disturbed.

Odaira¹⁴ reported that the basal metabolism becomes lower in the course of vitamin poor alimentation, although there is not a significant decrease, and again becomes higher when cardiovascular symptoms become marked.

To summarize. The important observations on the gas metabolism in vitamin B starvation are that a decrease occurs in the consumption of oxygen as well as in the production of carbon dioxide, that is, a lowering of the basal metabolism, in some instances, there is a marked decrease in the elimination of carbon dioxide, that is, a diminution of the respiratory quotient. In reviewing the protocols, however, the observations do

12 Yanagi, K. The Oxygen Consumption in Vitamin B Starvation, *Nippon Naika Gakukwai Zasshi* **13** 189, 1925, *Nippon Seikagakukai Kaiho* **1** 50, 1926.

13 Goh, T. *Nippon Byori Gakukwai Kaishi*, **15** 469, 1926.

14 Odaira, T. *Nissin Igaku*, **15** 1659, 1926.

not coincide, some even contradict each other, this is due perhaps to the conditions of the experiments and to the methods applied, but the most important factor is the difference in the materials employed. Perhaps we were the first to attempt a systematic investigation of gas metabolism in human beings during vitamin B starvation, although it was reported previously in one case by Caspari and Moszkowski. A detailed description of our observations therefore does not seem superfluous.

We made two series of investigations, one to determine the influence of vitamin B starvation on the basal metabolism in beriberi, the other to determine, if possible, whether any deviation in the gas metabolism may occur during the course of vitamin B starvation in normal persons.

METHOD

The material studied consisted of four patients with typical symptoms of beriberi and five healthy men. The patients with beriberi were examined carefully, and no complications were found with the exception of some parasites' eggs in the feces. The healthy subjects volunteered for the experiment. The diet for the patients with beriberi during the experiment was especially restricted. The main food consisted of well polished and thoroughly washed rice, the supplementary food consisted of beef, koyadofu, konvaku, fukujinzuke, lard, cane sugar, wheat meal, miso, soya and salts. The beef was boiled for two hours with 12 per cent caustic soda, it was then neutralized to a faintly acid reaction with acetic acid, and boiled. Konvaku was autoclaved from two to three hours at from 130 to 170 C. Food was selected which contained enough protein, fat, carbohydrate and salts. The meals were then adjusted to obtain the proper number of calories. For example, in case 1, breakfast consisted of 300 Gm of boiled rice, 30 Gm of miso, 10 Gm of fukujinzuke and one piece of koyadofu, lunch consisted of 300 Gm of boiled rice, one piece of koyadofu, 5 Gm of sugar, 20 cc of soya and 10 Gm of fukujinzuke and dinner consisted of 300 Gm of boiled rice, 100 Gm of beef, 10 Gm of lard, 10 Gm of wheat powder, 10 Gm of fukujinzuke and 10 Gm of salt, a total of 1,850 calories. The amount of protein in these meals was 79.3 Gm, fat, 25.3 Gm, and carbohydrate, 315 Gm. Vitamin B, however, was almost completely lacking, which was proved also by feeding pigeons with a pulverized mixture of these foods, as a consequence, a typical paralysis and convulsion occurred. Vitamin A (biosterin) was administered in liquid form. Three of the healthy subjects were fed on a relatively restricted diet, and all showed typical symptoms of avitaminosis after a period of incubation. Two others were fed on a slightly restricted diet which was not much different from the usual diet in the wards. After an observation of eighty-five and one hundred and twenty-three days, respectively, no symptoms were seen. Therefore, in these last two cases, although the vitamin B content was not rich, it was not deficient.

The metabolic rates were obtained by the gasometer method with analysis of the expired air by the Haldane gas analysis apparatus. The technic of Boothby and Sandiford was followed.

REPORT OF CASES

CASE 1—B. S., a youth, aged 15 years and 2 months, entered the hospital with a condition diagnosed beriberi. His family history was unimportant. He had had measles when a child, appendicitis at the age of 9, and some febrile disease at the age of 13 had confined him in bed for about one hundred days.

In the beginning of January, 1922, he felt numbness of the legs. On the 29th of that month, he was suffering from a cold, he had a mild headache and

a cough, his temperature was 39 C (102.2 F), and he was confined to bed. The fever continued until the middle of February. The numbness and hypesthesia extended up to the abdomen. Paralysis of the lower limbs developed, and the patient was unable to walk, but as the arms were not affected, he continued in his occupation (book-binding). On May 3 he visited the dispensary, and two days later he was admitted to the hospital.

Examination revealed a well nourished and vigorous man of medium height, somewhat pale. The pupillary reflexes were normal. The teeth and tonsils were in good condition. The tongue was rather dry and furred. Neither fever nor edema was present. The pulse rate was 80, it was strong, regular and moderately resistant to pressure. The thyroid gland was somewhat enlarged.

TABLE 1—*Metabolism Data on Patient with Beriberi (Case 1*)*

Date, 1922	Weight in Kg	Body-Surface (Du-Bois)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq Meter per Hr	Basal Metabolic Rate (Du-Bois)	Temperature, C	Diet and Medication of the Previous Day
5/25	48.8	1.46	80	20	0.74	47.9	+ 4.1	36.5	Usual diet
6/1	47.8	1.45	90	21	0.81	48.0	+ 4.3	36.6	Usual diet
6/5	48.5	1.46	100	16	0.80	45.8	- 0.4	36.4	Usual diet
6/20	45.0	1.41	75	14	0.76	43.3	- 5.8	36.5	Usual diet
7/13	46.2	1.43	82	19	0.78	42.1	- 8.5	36.4	Vitamin free 1 day
7/16	46.2	1.43	92	19	0.76	39.1	-15.0	36.3	Vitamin free 4 days
7/19	45.3	1.42	77	20	0.76	36.2	-21.3	36.5	Vitamin free 7 days
7/21	45.6	1.42	92	17	0.79	36.6	-20.4	36.6	Vitamin free 9 days
7/22	46.0	1.43	90	21	0.74	41.1	-10.6	36.4	Vitamin free + oryzanin powder 3.3 Gm + oryzanin solution 13.3 cc
7/26	45.7	1.42	72	19	0.75	41.5	- 9.8	36.2	Vitamin free + oryzanin solution 40 cc 1 day
8/1	45.7	1.42	86	20	0.96	46.1	+ 0.2	36.5	Vitamin free + oryzanin solution 40 cc 7 days
8/7	44.8	1.41	90	20	0.93	46.1	+ 0.2	36.5	Vitamin free + oryzanin solution 40 cc 13 days
8/9	44.8	1.41	78	22	0.94	37.6	-18.3	36.3	Vitamin free + autoclaved oryzanin 10 Gm 2 days
8/11	45.4	1.42	72	19	0.92	35.3	-23.2	36.4	Vitamin free + autoclaved oryzanin 10 Gm 4 days
8/13	45.4	1.42	68	20	0.81	38.1	-17.2	36.3	Vitamin free + autoclaved oryzanin 10 Gm 6 days
8/15	45.3	1.42	80	17	0.97	37.0	-19.6	36.2	Vitamin free + autoclaved oryzanin 10 Gm 8 days
8/17	45.4	1.42	88	17	0.97	36.6	-20.5	36.5	Vitamin free + autoclaved oryzanin 10 Gm 10 days
8/21	45.0	1.41	80	18	0.80	43.2	- 6.1	36.3	Vitamin free + oryzanin powder 10 Gm 3 days
8/25	45.9	1.42	70	20	0.92	43.1	- 6.3	36.4	Vitamin free + oryzanin powder 10 Gm 7 days
8/29	47.7	1.44	68	20	0.94	41.8	- 9.1	36.0	Vitamin free + oryzanin powder 10 Gm 11 days
9/13	46.3	1.43	72	21	0.94	42.7	- 7.2	36.4	Usual diet 5 days
9/17	45.9	1.42	92	18	0.85	41.7	- 9.3	36.2	Usual diet 9 days

* B. S., boy, aged 15 years and 2 months, 156.2 cm in height

There was a slight dulness over the right side of the collarbone. The heart was enlarged on both sides, the area of absolute dulness reached to the right sternal margin, to the upper margin of the fourth rib and the line of the left nipple. The systolic sound at the apex was somewhat impure, and the second pulmonic sound was slightly accentuated. The crural sound was rustling, and brachial sound was low and dull. The abdomen was somewhat distended. The liver was palpable two fingerbreadths under the costal arch and somewhat tender. There was no numbness, the arms were not affected, talipes equinus was present, motility of the lower limbs, especially the act of raising them, was impaired. Hypesthesia and hypalgia of the legs and the dorsa of the feet were noticeable, these areas were partly anesthetic. The sole was free from disturbances of sensibility. The knee and achilles reflexes were present. The cremasteric reflex was positive. The blood count showed 4,828,000 red blood cells, 80 per cent hemoglobin and 6,800 leukocytes, of which 45.2 per cent were polymorphonuclear neutrophils, 36 per

cent lymphocytes, 84 per cent eosinophils and 104 per cent mononuclears and transitory forms. The blood pressure was right side, systolic 141 and diastolic 0, left side, systolic 142 and diastolic 0.

The main clinical observations after vitamin B starvation (ten days' duration) were no marked change in weight, edema (\pm), no variation in the quantity of urine, loss of appetite since the fifth day and nausea on the sixth day. There was tenderness of the calf muscles before vitamin B starvation, which increased on the ninth to the eleventh day. The pulse rate had gradually increased since the third day, on the sixth day it was 126, on the tenth day 108 and on the fifth day distinctly dicrotic. The blood pressure just before the patient was placed on a restricted diet was right side, systolic 129 and diastolic 50, left side, systolic 132 and diastolic 62. On the third day the diastolic pressure began gradually to decrease, on the right side it was systolic 131 and diastolic 0, on the left, systolic 134 and diastolic 0. If the intensity of the crural sound before vitamin B starvation is expressed as +, on the sixth day it was ++ and on the ninth ++++. The brachial sound before the beginning of the restricted diet was —, on the sixth day and after vitamin B starvation, it was +. On the sixth day the patient became dyspneic, the heart was somewhat enlarged on both sides, there was accentuation of the second pulmonic sound, and the systolic murmur was louder. The chief changes were loss of appetite, greatly increased tenderness of the calf muscles, increased pulse rate (124), decrease in diastolic blood pressure, sharp crural sound and dicrotism. All these symptoms were significantly ameliorated after a vitamin B preparation was administered.

The average basal metabolism at the time the patient was on his usual diet was +0.2 per cent. During the nine days of the first experiment with vitamin B starvation, this average was —16.3 per cent, and during the period of administration of oryzanin it was —5 per cent. During the ten days of the second experiment with vitamin B starvation, the average metabolism was —19.8 per cent, and during the last period with vitamin B starvation or the usual diet, it was —7.6 per cent.

CASE 2—K. K., a man, aged 25, single, entered the hospital with a condition diagnosed beriberi. His paternal grandmother had died of apoplexy at the age of 72, his father had died of nephritis at 69, and his mother had died of an unknown disease at 63. The patient had four brothers and sisters, all of whom were healthy. A nephew had died of acute decompensation (cardiac form of beriberi). The patient had had measles when a child, otherwise he had always been healthy. In June, 1926, he returned from military service, and resumed his work as a peasant. His main food was polished rice. During the latter part of August the patient felt numbness of the legs, weakness of the calf muscles, especially when walking, and looseness of the knee joints, so that he tired readily. Edema appeared over the tibia and the dorsa of the feet. In the middle of September palpitation and dyspnea appeared on movement, and he was unable to walk. On September 16 the symptoms were aggravated, and decompensation appeared, accompanied by oppression, nausea, eructation and vomiting. He became unconscious, from which state he fortunately recovered. On November 6 he again had decompensation and was confined to his bed for about thirty days. He could walk a little during the latter part of December. In March of this year he again worked in the field, after which he felt weak and noticed edema. He was admitted to the hospital on June 3.

Examination revealed a well nourished and vigorous man of medium height. A slight cyanosis of the lips and fingertips was present. The pupillary reflexes were normal. The tongue was moist and slightly furred. He had a tremor. The pulse rate was 75, it was regular and moderately resistant to pressure. The blood pressure was 126 systolic and 62 diastolic, and did not indicate that sclerosis was present. Respiration was 22, regular and of the costo-abdominal type. Expiration at the right apex of the lung was somewhat prolonged and high pitched. The apex beat was diffuse and heaving. (The left border of the heart was one-half fingerbreadth inside of the nipple line.) The systolic sound at the apex was somewhat dull, the second pulmonic sound was slightly accentuated and if it

occurred coincident with expiration, it was split. The crural sound was audible. The gait was wide and waddling. There was hypesthesia from the costal arch and from the middle of the back downward. The epigastric and cremasteric reflexes were positive. Knee and achilles reflexes were present. The tenderness of the calf muscles was significant. Edema was not present. Urinalysis showed a specific gravity of 1.027, and a urine the color of beer and slightly alkaline. The sulphosalicylic test was opalescent, the indican test was negative. The blood count showed 5,740,000 red blood cells, 95 per cent hemoglobin and 7,500 leukocytes, of which 67.5 per cent were polymorphonuclear neutrophils, 21 per cent lymphocytes, 8 per cent eosinophils, 0.5 per cent basophils and 3 per cent mononuclears and transitory cells.

The main clinical observations after vitamin B starvation (seven days' duration) were: A slight decrease in weight, edema, a sudden decrease in the quantity of urine from 1,600 cc to 200 cc. The patient lost his appetite on the fifth day, and nausea and vomiting occurred three times on the sixth day. Flaccidity and tenderness of the calf muscles appeared. The pulse rate had gradually increased.

TABLE 2—*Metabolism Data on Patient with Beriberi (Case 2*)*

Date, 1922	Weight in Kg	Body- Sur- face (Du- Bois)	Res- pira- tion Rate	Res- pira- tory Quo- tient	Calo- ries per Sq Meter per Hr	Basal Metabolic Rate (Du- Bois)	Tem- pera- ture, C	Diet and Medication of the Previous Day
6/29	58.5	1.59	90	0.71	41.2	+4.3	36.7	Usual diet
6/30	58.4	1.58	84	0.75	40.9	+3.5	36.2	Usual diet
7/4	59.1	1.59	80	0.74	41.6	+5.5	36.2	Usual diet
7/10	58.7	1.59	75	0.79	41.6	+5.5	36.2	Usual diet
7/13	57.8	1.57	69	0.72	39.1	-1.0	35.8	Vitamin free 1 day
7/16	57.8	1.57	76	0.74	37.8	-4.3	36.2	Vitamin free 4 days
7/18	57.0	1.56	86	0.68	35.8	-9.4	37.2	Vitamin free 6 days
7/21	58.8	1.58	75	0.90	37.5	-5.1	37.0	Vitamin free + spelzon 40 cc
7/26	57.8	1.57	64	0.81	41.8	+5.8	36.5	Vitamin free + spelzon 40 cc
8/1	55.5	1.55	62	0.77	42.3	+7.1	36.1	Vitamin free + spelzon 40 cc
8/3	55.9	1.55	38	0.73	33.6	-2.3	36.1	Vitamin free 2 days
8/5	55.5	1.55	64	0.74	37.5	-5.1	36.0	Vitamin free 4 days
8/7	56.0	1.55	66	0.77	33.7	-14.7	36.3	Vitamin free 6 days
8/9	56.2	1.55	70	0.93	31.4	-20.5	36.5	Vitamin free 8 days
8/11	56.8	1.56	78	0.90	32.4	-17.9	36.4	Vitamin free 10 days
8/13	57.7	1.57	68	0.78	35.0	-11.4	36.3	Diet with vitamin
8/14	57.9	1.57	66	0.78	38.8	-1.7	36.2	Diet with vitamin
8/19	58.3	1.58	70	0.93	39.7	+0.5	35.8	Usual diet
8/23	58.1	1.58	84	0.81	40.0	+1.3	36.3	Usual diet

* K. K., man, aged 25, 156.3 cm. in height.

since the fourth day, on the sixth day it was 110. The blood pressure before the patient was placed on a restricted diet was 116 systolic and 30 diastolic on the right side, and 109 systolic and 68 diastolic on the left, on the fifth day it was 99 systolic and 0 diastolic on the right, and 99 systolic and 40 diastolic on the left. The crural sound became sharp, the brachial sound before the restricted diet was not heard, on the fifth day it was audible. Palpitation before vitamin B starvation did not occur, on the fourth day there was palpitation even when the patient was in bed. The heart was somewhat enlarged. The chief changes were diminution in the quantity of urine, loss of appetite, vomiting, increased pulse rate and sharp crural sound.

The average basal metabolism diminished during vitamin B starvation. When the patient was on his usual diet, the average basal metabolism was +4.5 per cent, during the seven days of the first experiment with vitamin B starvation, this average was -4.8 per cent, and during the period of vitamin B medication it was -2.5 per cent. During the second experiment, when the patient did not receive any vitamins, the average metabolism was -12.1 per cent, and when he received a vitamin B preparation or the usual diet it was -2.8 per cent.

CASE 3—S. A., a man, aged 22, was admitted to the hospital with a condition diagnosed beriberi. His family history was unimportant. He had had measles when a child and had been vaccinated many times. During the latter part of

April, 1926, the patient suffered from distention and a full sensation at the epigastrium, sometimes nausea, vomiting and pain in the region of the stomach. The appetite was deficient. About the middle of May he returned to his home, and the symptoms became milder. He was admitted to the hospital on July 30, after his symptoms had been more severe for five or six days.

Examination revealed a well nourished and vigorous man, somewhat small, the subcutaneous fat tissue was well developed, and the expression was natural. He had cyanosis and tremor at the fingertips. The tongue was moist and coated. Dermography was present. The pulse was normally resistant to pressure, strong

TABLE 3—Metabolism Data on Patient with Beriberi (Case 3*)

Date, 1922	Weight in Kg.	Body Surface (Du Bols)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq Meter per Hr	Basal Metabolic Rate (Du Bols)	Temperature, C	Diet and Medication of the Previous Day
8/ 7	48.8	1.11	60	16	0.89	29.8	+ 0.8	36.5	Usual diet
8/ 8	48.1	1.11	64	15	0.90	40.7	- 2.3	36.2	Usual diet
8/16	48.5	1.11	58	15	0.83	10.2	- 1.8	6.2	Vitamin free + oryzanin 4.5 Gm 1 day
8/18	47.3	1.12	70	16	0.76	37.7	- 1.5	36.9	Vitamin free + oryzanin 4.5 Gm 3 days
8/22	47.1	1.12	56	15	0.79	37.7	- 4.5	35.9	Vitamin free + oryzanin 6 Gm 3 days
8/24	47.3	1.12	56	15	0.90	31.1	-13.6	35.0	Vitamin free + autoclaved oryzanin 6 Gm 2 days
8/26	47.7	1.13	60	19	0.93	32.8	-16.9	36.0	Vitamin free + autoclaved oryzanin 6 Gm 4 days
8/28	47.0	1.12	60	20	0.85	36.0	- 8.8		Vitamin free + autoclaved oryzanin 6 Gm 6 days
8/30	47.1	1.12	58	15	0.82	31.1	-16.2	35.7	Vitamin free + autoclaved oryzanin 6 Gm 8 days
9/ 1	46.8	1.12	60	13	0.78	29.8	-22.0	36.4	Vitamin free + autoclaved oryzanin 6 Gm 10 days
9/ 3	46.4	1.12	60	14	0.78	32.9	-16.7	36.1	Vitamin free + autoclaved oryzanin 6 Gm 12 days
9/ 5	46.7	1.12	66	14	0.81	31.8	-10.5	36.1	Vitamin free + autoclaved oryzanin 6 Gm 14 days
9/ 7	46.5	1.12	60	13	0.82	31.7	-19.7	36.1	Vitamin free + autoclaved oryzanin 6 Gm 16 days
9/ 9	46.2	1.11	60	22	0.79	32.4	-17.9	35.9	Vitamin free + autoclaved oryzanin 6 Gm 18 days
9/11	46.0	1.11	65	13	0.82	32.9	-16.7	36.1	Vitamin free + autoclaved oryzanin 6 Gm 20 days
9/13	46.0	1.11	62	18	0.78	26.1	-33.9	6.3	Vitamin free + autoclaved oryzanin 6 Gm 22 days
9/15	45.0	1.39	60	13	0.74	36.1	- 8.6	35.5	Vitamin free + oryzanin 6 Gm 2 days
9/17	45.5	1.40	60	11	0.73	36.3	- 8.1	35.4	Vitamin free + oryzanin 6 Gm 4 days
9/19	45.7	1.10	56	20	0.76	37.1	- 6.1	6.1	Vitamin free + oryzanin 6 Gm 6 days
9/21	45.7	1.40	66	14	0.76	37.1	- 6.1	36.0	Vitamin free + oryzanin 6 Gm 8 days
9/24	45.8	1.40	60	13	0.72	35.8	- 1.7	36.1	Vitamin free + milk 300 cc 2 days
9/28	46.0	1.41	64	12	0.83	37.1	- 6.1	36.3	Vitamin free + milk 300 cc 6 days

* S. A., man, aged 22, 153.7 cm. in height.

and regular, the blood vessels were neither sclerotic nor tortuous. The respiration was of the costo-abdominal type. The apex beat was scarcely noticeable, one fingerbreadth inside of the nipple line in the fifth intercostal space. The area of absolute dullness extended from the left sternal margin to the upper edge of the fourth rib and the line of the left nipple, the area of relative dullness extended from the right sternal margin to the upper edge of the third rib and half a fingerbreadth outside of the nipple line. At the apex the first sound was impure, the second pulmonic sound was accentuated and split (by inspiration). The crural and brachial sounds were not distinctly audible. The knee reflexes were weak, and the achilles reflex was present. Motility was not affected. During the latter part of April hypesthesia appeared, and in June it extended from the toes to the middle of the abdomen. The sole of the foot was not affected.

The main clinical observations after vitamin B starvation (twenty-two days' duration) were a slight decrease in weight (about 1 Kg), absence of edema and slight variation in the quantity of urine. The patient was constipated (once for four days), he lost his appetite on the fifth day, general flaccidity and dulness had been present since the sixth day and numbness since the fourth day. There was no marked change in the pulse rate, the blood pressure was without significance. The crural sound had been noticeable since the seventh day and the brachial sound since the tenth day. The chief changes were constipation, increased tenderness of the calf muscles and exaggeration of the vessel sounds.

The average basal metabolism during the time the patient was on his usual diet was -1 per cent, during vitamin B starvation -18.5 per cent and during the time of vitamin B medication or when the patient drank milk -6.1 per cent.

CASE 4—M O, a man, aged 22, was admitted to the hospital on Aug 17, 1926, with a condition diagnosed beriberi. The family history was unimportant. The patient had had measles when a child and had been vaccinated many times. At the age of approximately 10 years, he suffered from pleurisy after falling from a tree. At the age of 19, he suffered from influenza and was in bed for about three days. Both tonsils had been removed in 1926. Defecation occurred once every day. Early in June he had felt numbness and heaviness of the dorsa of the feet, and in the beginning of August there was numbness of the fingertips. The looseness of the knee caused him to fall. He did not experience thirst, but he perspired occasionally, and there was no edema.

The patient was moderately nourished, his expression was natural. He was not anemic. The tongue was clean, moist and without tremor. The face and the body were dry, but the dorsa of the feet were moist. The pupillary reflex was positive. Respiration was of the costo-abdominal type. There was no sclerosis of the vessels. The apex beat was in the fifth intercostal space on the nipple line. The area of relative dulness extended from one and one-half fingerbreadths outside of the right sternal margin to the upper edge of the third rib and half a fingerbreadth beyond the line of the left nipple. The second pulmonic sound was accentuated, and the first sound at the apex was impure. The crural sound was sharp but not loud, with a murmur, the brachial sound was audible with a murmur. The right arm was somewhat weaker than the left. The mucous membrane was not affected. Knee jerks were present, the achilles reflex on the right side was doubtful, on the left, absent. The calf muscles, especially on the inner side, were somewhat hard, there was no edema or glandular swelling, the right kidney was palpable. Urinalysis showed specific gravity, 1.031, a reddish-yellow and acid urine, no protein or sugar, indican $++$. In the blood, there were 4,590,000 red blood cells, 90 per cent hemoglobin and 5,200 leukocytes, of which 53.2 per cent were polymorphonuclear neutrophils, 36.5 per cent lymphocytes, 6.2 per cent eosinophils, 0.2 per cent basophils and 4.7 per cent transitory cells.

The main clinical observations after vitamin B starvation (thirteen days' duration) were a slight increase in weight during the beginning, no edema, no variation in the quantity of urine, defecation once a day until the third day, when constipation and loss of appetite occurred. Tenderness of the calf muscles since the third day was $+$, and since the tenth day $++$. The chief changes were constipation, loss of appetite and tenderness of the calf muscles.

The average metabolism during the times the diet was free from vitamin B and the patient was receiving vitamin B preparation was $+2.5$ per cent, during vitamin B starvation it was -13.7 per cent and with vitamin B preparation or with milk it was -5.8 per cent.

From the foregoing descriptions it can be seen that the four patients with beriberi always showed more or less aggravation of symptoms after vitamin B starvation, especially when the cardiovascular system was mainly involved (cases 1 and 2). The danger of decompensation made

further continuance of the avitaminous alimentation dangerous. In all cases the basal metabolism showed distinct decrease during vitamin B starvation (without vitamin or with autoclaved, that is, destroyed vitamin) and increase after the addition of vitamin. The respiratory quotient showed no remarkable change during the course of the vitamin B starvation. There was loss of appetite in all cases, and the intake of food was diminished, but the decrease in basal metabolism

TABLE 4—*Metabolism Data on Patient with Beriberi (Case 4*)*

Date, 1922	Weight in Kg	Body Surface (Du Bols)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq Meter per Hr	Basal Metabolic Rate (Du Bols)	Temperature, C	Diet and Medication of the Previous Day
8/21	47.1	1.47	56	21	0.78	40.2	+ 1.7	36.1	Vitamin free diet -- oryzanin 6 Gm
8/23	47.1	1.47	55	23	0.80	40.7	+ 3.0	36.2	Vitamin free diet + oryzanin 6 Gm
8/25	47.6	1.47	60	22	0.78	36.1	-- 5.6	35.8	Vitamin free diet + autoclaved oryzanin 6 Gm 2 days
8/27	47.5	1.47	58	22	0.81	34.2	-- 13.4	35.9	Vitamin free diet + autoclaved oryzanin 6 Gm 4 days
8/29	47.0	1.47	60	21	0.90	32.6	-- 17.1	36.7	Vitamin free diet -- autoclaved oryzanin 6 Gm 6 days
8/31	46.3	1.46	66	17	0.75	34.7	-- 12.2	36.0	Vitamin free diet -- autoclaved oryzanin 6 Gm 8 days
9/ 2	46.2	1.46	65	18	0.87	32.7	-- 17.2	36.9	Vitamin free diet -- autoclaved oryzanin 6 Gm 10 days
9/ 4	47.2	1.47	70	18	0.87	34.2	-- 17.4	36.9	Vitamin free diet -- autoclaved oryzanin 6 Gm 12 days
9/ 6	47.2	1.47	61	20	0.85	35.6	-- 9.3	36.0	Vitamin free diet -- oryzanin 6 Gm
9/ 8	46.3	1.46	58	10	0.82	37.3	-- 5.6	36.0	Vitamin free diet -- oryzanin 6 Gm
9/10	45.8	1.45	46	11	0.78	35.0	-- 11.1	35.4	Vitamin free diet + oryzanin 10 Gm
9/12	44.8	1.44	44	16	0.87	36.6	-- 7.3	35.7	Vitamin free diet + oryzanin 10 Gm
9/14	43.2	1.42	40	18	0.77	32.4	-- 2.9	35.7	Vitamin free diet + oryzanin 10 Gm
9/16	42.6	1.41	42	15	0.75	37.5	-- 5.1	35.7	Vitamin free diet + oryzanin 10 Gm
9/18	42.6	1.41	72	17	0.76	34.8	-- 11.9	35.3	Vitamin free diet + oryzanin 10 Gm
9/20	42.8	1.41	45	17	0.90	34.4	-- 12.9	35.7	Vitamin free diet + oryzanin 10 Gm
9/22	42.8	1.41	45	19	0.78	37.9	-- 4.0	35.7	Vitamin free diet + oryzanin 10 Gm
9/24	43.0	1.41	44	19	0.90	40.4	+ 2.3	36.0	Vitamin free diet + oryzanin 10 Gm
9/26	43.3	1.42	50	15	0.85	40.3	+ 2.0	36.2	Vitamin free diet + milk 600 cc
9/28	43.2	1.42	48	12	0.96	40.7	+ 3.0	36.2	Vitamin free diet + milk 600 cc

* M. O., man, aged 21, 161 cm in height

was proved to occur at the time when the intake of food was still sufficient, or when a great deal of nourishment was taken on the previous day. The body weight was slightly diminished in one case (1 Kg), while in others there was some increase, partly the result of edema. Therefore decrease in basal metabolism is not to be attributed to simple starvation, it seems to have an intimate relation to deficiency in vitamin B. The foregoing experiments are not sufficient to decide this question, healthy persons should be subjected to long continued vitamin B starvation until typical symptoms of avitaminosis develop, and the variation in basal metabolism should be noted. As we found that a

diet which induces avitaminosis soon causes a loss of appetite, it seems reasonable to arrange a diet which is slightly restricted, but which does not contain sufficient vitamin B. The research in cases 5 to 9 was carried out for this purpose.

CASE 5—S. A., a man, aged 25, single, a healthy peasant, whose family history was unimportant, had had measles when a child, and had been vaccinated many times. His history was not suggestive of beriberi. He took sake (Japanese wine), about two glasses (400 cc) occasionally, and used tobacco (twenty cigarettes a day).

The patient was well nourished and vigorous and of medium height. The pupillary reflexes were normal. The tongue was moist and clean, and the left tonsil was somewhat enlarged. The pulse rate was 72, it was regular and moderately resistant to pressure. Respiration was 19 and was costo-abdominal in type.

TABLE 5—*Metabolism Data on Healthy Patient (Case 5*)*

Date, 1923	Weight in Kg	Body-Surface (Du Bois)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq Meter per Hr	Basal Metabolic Rate (Du Bois)	Temperature, C	Diet and Medication of the Previous Day
12/ 2	50.6	1.48	53	14	0.79	38.9	-1.5	36.3	Usual diet
12/ 3	51.0	1.49	56	16	0.77	41.0	+3.7	36.3	Usual diet
12/12	49.9	1.48	51	23	0.74	41.3	+4.5	36.3	Usual diet
12/13	50.0	1.48	52	23	0.75	43.1	+8.9	36.5	Usual diet
12/22	49.6	1.47	56	19	0.95	35.5	-10.1	36.2	Vitamin poor diet 9 days
12/26	49.8	1.48	56	16	0.91	37.6	-5.0	36.3	Vitamin poor diet 13 days
12/27	49.6	1.47	53	18	0.90	35.7	-9.7	36.2	Vitamin poor diet 14 days
1924									
1/12	50.0	1.48	60	16	0.79	36.6	-7.3	36.4	Vitamin poor diet 30 days
1/16	50.8	1.48	56	28	0.74	38.3	-3.1	36.3	Vitamin poor diet 34 days
1/17	51.3	1.49	59	18	0.83	35.0	-11.4	36.4	Vitamin poor diet 35 days
2/ 2	51.1	1.49	55	22	0.81	24.3	-37.0	36.1	Vitamin poor diet 51 days
2/16	51.8	1.50	58	25	0.70	31.6	-20.0	36.8	Vitamin poor diet 65 days
2/25	52.4	1.51	71	21	0.83	38.6	-2.3	37.2	Vitamin poor diet 72 days
3/ 1	52.8	1.51	62	23	0.79	36.8	-6.7	36.4	Vitamin poor diet 78 days
3/ 8	53.5	1.52	66	24	0.66	38.3	-3.0	36.3	Vitamin poor diet, 85 days
3/15	55.0	1.54	72	21	0.71	38.4	-2.8	36.3	Vitamin poor diet 92 days
3/20	53.9	1.53	80	23	0.72	38.5	-2.6	36.1	Vitamin poor diet 97 days
3/23	53.3	1.52	53	20	0.78	42.9	+9.0	36.0	Vitamin poor diet with vitamin B 3 days
3/28	52.1	1.50	60	19	0.75	46.2	+14.5	36.2	Vitamin poor diet with vitamin B 8 days
4/ 5	53.1	1.52	60	20	0.87	42.9	+8.7	36.5	Usual diet 5 days

* S. A., man, aged 26, 156.5 cm in height.

The right apex was somewhat dull, expiration was prolonged. The area of absolute dullness extended from the midline to the lower edge of the fourth rib and one fingerbreadth inside of the line of the left nipple, the area of relative dullness extended from the right sternal margin to the lower edge of the third rib and just inside of the nipple line. The liver was palpable, but no abnormalities were found. Sigmoides was also palpable. The abdominal and cremasteric reflexes were normal. The knee and achilles reflexes were slightly exaggerated. Urinalysis showed specific gravity 1.019. The urine was slightly acid, it did not contain protein, sugar or indican, but a moderate number of granulated casts, leukocytes, tailed and pavement epithelia were found. Eggs of parasites (*Ankylostoma*, *Trichostrongylus orientalis* and *Trichocephalus dispar*) were present in the feces.

Beginning Dec 13, 1923, a vitamin poor diet was administered. For example, the breakfast consisted of 500 Gm of boiled rice, 30 Gm of miso, 400 cc of tea without sugar, lunch consisted of 500 Gm of boiled rice, 35 Gm of tofukara, 15 Gm of onion, 4 Gm of aburag , 7 cc of soya and 200 cc of tea, dinner consisted of 500 Gm of boiled rice, 50 Gm of green vegetable, 15 Gm of fish, 15 cc of soya, 3 Gm of sugar and 500 cc of tea. The rice was continued

every day in the same way, the accessory diet was changed somewhat, but within the limitations every day

About the end of January, 1924 (about forty days after the patient was first placed on the vitamin poor diet), slight symptoms began to appear, such as tenderness of the calves, slight cramp in the right knee and slight heartburn. In the beginning of February the symptoms became especially significant. The heart was enlarged to the left (on the left border the area of absolute dulness was half a fingerbreadth inside of the nipple line, the area of relative dulness was at the nipple line). A systolic murmur was marked at the apex and tricuspidal ostium, the second pulmonic sound was slightly accentuated and split. When the patient was in the recumbent posture, the second pulmonic sound was distinctly accentuated, the systolic murmur was audible in all valve areas, being especially marked at the apex and in the tricuspid area. There was slight edema of the face and over the tibia, which from time to time became moderately significant. Transient tenderness of the ribs (from the seventh to the tenth) was also observed. On March 1, hypesthesia appeared on the inner side of the legs. The heart was enlarged on both sides and to the upper border. The crural sound was sharp. Weakness of the leg was noticed, but there was no disturbance of motility or coarse motion. Symptoms of the stomach and the intestine were not significant. The pulse rate was 72, it was regular, not soft and not fast. In the middle of March symptoms, such as a full sensation and heartburn appeared. Beginning on March 20, vitamin B preparation was administered. When the patient was sitting, the area of absolute dulness extended from the right sternal margin to the lower edge of the third rib and one-half fingerbreadth outside of the nipple line. The first tricuspidal and apex sound was impure and loud, the second aortic sound was accentuated. With vitamin B administration, there began to be relief from the symptoms. On April 10, the apex beat was one fingerbreadth inside of the line of the left nipple, the right border and the upper border were just as before, and the left border was just inside (absolute) and just outside (relative) of the nipple line. The heart sounds were all pure, the first aortic and the pulmonic sound were split. The liver was palpable one fingerbreadth under the right costal arch. The knee and achilles reflexes were exaggerated as before. Chaddock's sign was negative, there was no tenderness of the calves or edema. There were no disturbances of sensibility and no abnormalities in the urine.

The average basal metabolism when the patient was on his regular diet was +4 per cent, in vitamin B starvation it was -81 per cent, and with vitamin B medication, or when the regular diet was resumed, it was +114 per cent. During the period of vitamin B starvation, there was a distinct lowering of the basal metabolism.

CASE 6—T N, a man, aged 28, was a healthy person whose family history was unimportant. The patient had had measles when a child, and had been vaccinated many times. At the age of 17, he had had syphilis and gonorrhea, but was not treated. The next year, he suffered from diphtheria, and thereafter was inclined to pharyngeal inflammation. He had also suffered from pneumonia about ten years before, from a disorder of the stomach about six years before and from typhoid fever in June, 1926. He took Japanese wine occasionally (200 cc) and used tobacco moderately. He had suffered from hernia inguinalis sinistra since childhood. He did not cough and did not raise sputum. He had worked at home as a peasant since childhood. He had not been in military service.

The patient was a well nourished and vigorous man somewhat short. His expression was natural. Moderate cyanosis and anemia were present. The tongue was moist and clean, the arch of the palate was congested. The muscles were well developed. The pulse rate was 82, it was rather low, soft and regular. Respiration was of the costo-abdominal type. The pupillary reflexes were normal. The right apex was somewhat dull, expiration was sharp and prolonged, there was sparse crepitation at both apexes. The area of absolute dulness was from the midline to the lower edge of the fourth rib and one and one-half fingerbreadths inside the nipple line, the area of relative dulness extended from the

right sternal margin to the lower edge of the third rib and one-half fingerbreadth inside of the nipple line. The first sound at the apex was hollow. When the patient was in a recumbent posture, a slight systolic murmur was audible at all valve areas. The second pulmonic sound was accentuated and split. The blood pressure was 108 systolic and 40 diastolic. Sensibility and motility were not affected. There was nothing unusual about the abdomen. The knee jerks were exaggerated, and the achilles reflex was normal. There were no abnormalities in the urine. Eggs of *Ankylostoma* and *Ascaris* were detected in the feces. The blood count showed 5,700,000 red blood cells, 65 per cent hemoglobin and 5,700 leukocytes, of which 62 per cent were polymorphonuclear neutrophils, 38.6 per cent lymphocytes, 4.8 per cent eosinophils, 0.4 per cent basophils and 2.4 per cent mononuclears.

Beginning Nov 23, 1923, vitamin poor diet was administered as in case 5.

In the middle of December the patient complained of heartburn, eructation and a feeling of palpitation in the region of the stomach. He felt disgusted and

TABLE 6—Metabolism Data on Healthy Patient (Case 6)

Date, 1923	Weight, Kg	Body-Surface (Du Bois)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq Meter per Hr	Basal Metabolic Rate (Du Bois)	Temperature, C	Diet and Medication of the Previous Day
11/13	48.6	1.43	60	17	0.95	40.7	+ 3.0	36.1	Usual diet
11/17	48.8	1.44	61	17	0.79	41.8	+ 3.5	36.9	Usual diet
11/21	48.4	1.43	55	19	0.80	38.8	- 1.8	36.5	Usual diet
11/30	48.7	1.44	57	21	0.92	40.0	+ 1.8	36.8	Vitamin poor diet 7 days
12/1	48.9	1.44	57	18	0.92	36.8	- 6.7	36.7	Vitamin poor diet 8 days
12/14	48.3	1.43	65	18	0.69	36.0	- 8.9	36.4	Vitamin poor diet 21 days
12/15	48.5	1.43	56	18	0.75	35.5	-10.1	36.7	Vitamin poor diet 22 days
12/21	48.6	1.43	54	17	0.81	34.5	-13.0	36.5	Vitamin poor diet 28 days
12/22	48.6	1.43	62	14	0.82	36.5	- 7.6	36.5	Vitamin poor diet 29 days
12/25	48.1	1.43	67	15	0.88	36.7	- 7.0	36.9	Vitamin poor diet 63 days
1924									
2/7	46.6	1.41	68	16	0.88	32.2	-18.6	36.3	Vitamin poor diet + vitamin B 7 days
2/13	47.1	1.42	63	15	0.89	31.4	-20.7	36.7	Vitamin poor diet + vitamin B 13 days
2/21	47.6	1.42	66	19	0.90	36.7	- 7.2	36.1	Vitamin poor diet + vitamin B 21 days
3/1	47.4	1.42	66	15	0.75	38.3	- 0.6	36.6	Vitamin poor diet + vitamin B 29 days
3/8	47.3	1.42	62	14	0.75	37.8	- 4.0	36.5	Vitamin poor diet + vitamin B 36 days
3/15	48.3	1.43	70	18	0.78	40.6	+ 2.8	36.6	Vitamin poor diet + vitamin B 43 days
4/5	47.8	1.42	64	19	0.81	38.0	- 3.7	36.7	Usual diet 15 days

* T. N., male, aged 28, 153 cm in height.

nauseated when he saw food. In the middle of January, 1924, when he touched himself while bathing, the patient had a sensation as if paper had been drawn across the inside of the lower part of the legs and under the umbilicus. He complained of a looseness of the knee and slight bladder tenesmus. The symptoms of avitaminosis had become evident. The calves ached when he walked or when he moved his hip joints, and the stretching and bending power of the knee was weakened. During the latter part of January, the symptoms developed significantly. The patient complained of continued nausea, tenderness of the quadriceps and gastrocnemius, neuralgic pain and tenderness of the intercostal spaces and of the outer part of the upper part of the legs. He had developed a wide gait, and the raising of the toes was difficult. Slight edema appeared over the tibia. The patient complained of palpitation, the pulse rate was strong and fast, about 120 while the patient was sitting. Carotid pulsation when the patient was in a recumbent posture was significant. The liver was palpable one fingerbreadth under the right costal arch. The area of absolute dulness 0.5 cm extended from the right of the right sternal margin to the lower edge of the third rib and the line of the left nipple, the area of relative dulness extended from

one fingerbreadth to the right of the right sternal margin to the upper edge of the third rib and 0.5 cm outside the nipple line. The first sound at the apex was impure and weak, a systolic murmur was noted at the pulmonic ostium, and the second pulmonic sound was accentuated and split. The crural sound was sharp and accompanied by a systolic murmur. Plantar flexion of the right foot was somewhat weakened, dorsal flexion on both sides was weakened. The knee jerks on both sides were exaggerated. Beginning January 30, vitamin B preparation was administered. The symptoms became less marked, and on March 11, the heart border showed absolute dullness from the right sternal margin to the upper edge of the third rib and one fingerbreadth outside the nipple line. At the apex, the first and second sounds were hollow, the second pulmonic sound was split, but was no longer accentuated. At the beginning of April all symptoms were markedly ameliorated, and on the 21st of that month the patient left the hospital.

The basal metabolism at the time the patient was on his regular diet was +2.3 per cent, during vitamin B starvation it was -7.3 per cent, with vitamin B

TABLE 7—*Metabolism Data on Healthy Patient (Case 7*)*

Date, 1923	Weight in Kg	Body-Surface (Du-Bois)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq Meter per Hr	Basal Metabolic Rate (Du-Bois)	Temperature C	Diet and Medication of the Previous Day
12/ 2	51.5	1.77	74	16	0.82	41.6	+ 5.3	37.8	Usual diet
12/ 3	51.3	1.76	71	14	0.89	37.1	- 6.1	36.4	Usual diet
12/12	53.4	1.84	69	17	0.67	41.6	+ 5.3	36.4	Usual diet
12/22	53.1	1.81	81	16	0.86	40.9	+ 3.6	36.1	Vitamin poor diet 9 days
12/27	53.5	1.85	79	11	0.91	39.2	- 0.8	36.2	Vitamin poor diet 14 days
12/29	53.5	1.85	67	20	0.63	38.5	- 2.5	36.3	Vitamin poor diet 16 days
1924									
1/12	54.1	1.85	70	14	0.77	40.3	+ 2.0	36.7	Vitamin poor diet 39 days
1/16	54.8	1.87	85	16	0.86	40.6	+ 2.8	36.3	Vitamin poor diet 34 days
1/27	54.5	1.87	83	15	0.75	40.3	+ 2.0	36.3	Vitamin poor diet 45 days
2/ 2	55.2	1.88	81	16	0.83	39.9	-14.2	36.3	Vitamin poor diet 51 days
2/ 9	55.9	1.89	85	17	0.75	40.9	+ 3.5	36.1	Vitamin poor diet 58 days
2/16	56.5	1.89	81	17	0.68	39.3	-10.7	36.6	Vitamin poor diet 65 days
2/23	54.9	1.87	71	16	0.67	38.7	- 2.0	36.1	Vitamin poor diet 72 days
2/28	52.3	1.83	73	11	0.61	37.5	- 5.0	37.7	Vitamin poor diet 77 days
3/ 4	52.6	1.83	78	16	0.68	31.6	-20.0	36.3	Vitamin poor diet 83 days
3/ 8	49.6	1.80	75	16	0.76	35.3	-10.7	36.9	Vitamin poor diet - vitamin B 4 days
3/14	54.5	1.87	70	17	0.88	36.5	- 7.5	35.4	Vitamin poor diet + vitamin B 10 days
3/18	49.8	1.80	70	17	0.71	44.5	+17.8	36.3	Vitamin poor diet + vitamin B 11 days
4/11	46.3	1.45	62	21	0.72	50.1	+27.5	36.7	Usual diet 18 days

* T I, man, aged 24, 160 cm in height

medication or when the usual diet was resumed, it was -7.3 per cent. The last low value was due to the fact that it was low at the beginning of this period, gradually becoming higher later.

CASE 7—T I, a man, aged 23, single, a healthy person, was admitted to the hospital on Nov 29, 1923. His family history was unimportant. He had had measles at the age of 7 and had been vaccinated many times. When he was 21 years of age, he worked as ironsmith in a factory from January to the following April. It was hard work, and he was obliged to stand usually for about ten hours every day. In July and August he noticed a slight edema over the tibia in the evening, which had disappeared the next morning after rest in bed. During the autumn this condition was not noticeable. Since April, 1926 he had been engaged again in agriculture, working about eight hours a day. In October an operation for hemorrhoids was performed, otherwise he had always been healthy. He took no alcohol, but used tobacco moderately.

The patient was a well nourished and vigorous man. The pupillary reflexes were normal, the tongue was moist, not furred and without tremor. The left tonsil was slightly enlarged and injected. The skin was normal. The muscles

were well developed. The pulse rate was somewhat low and weak, but regular. Respiration was of the costo-abdominal type. The right apex was slightly dull, and expiration was prolonged. At the lower part of the back on the right side the respiration murmur was somewhat weaker than on the left side. The area of absolute dullness extended from the midline to the lower edge of the fourth rib and two fingerbreadths inside the left nipple line; the area of relative dullness extended from the right sternal margin to the lower edge of the third rib and one-half fingerbreadth inside the nipple line. The first sound at the apex was somewhat impure, otherwise nothing of importance was noted. Motility and sensibility were not affected. The urine was normal. Eggs of *Inkylostoma* and *Trichocephalus* were detected in the feces. Beginning Dec. 13, 1923, the patient was placed on a vitamin poor diet (nearly the same as that in cases 5 and 6).

On Jan. 20, 1924 (about a month after the beginning of the vitamin poor diet), the lower part of the abdomen and both calves became slightly hypesthetic. The condition had grown significant at the end of that month. A trace of edema over the tibia, tenderness of the calves, weakness of the knee and achilles reflexes appeared. The crural sound was hollow, but distinctly reduplicated, the second pulmonary sound was accentuated when the patient was in a sitting position. At the beginning of February, the heart border was enlarged to the right side; the area of absolute dullness was the right sternal margin. There was a slight enlargement to the left (one and one-half fingerbreadths inside the nipple line). A systolic murmur was noticed at all valve areas when the patient was in a sitting position. When the patient was in a recumbent position the second pulmonary sound was accentuated and impure. The pulse rate was 90, and it was strong, rapid, diastolic and soft. The patient stumbled often while walking. The joint of the knee slipped. The right knee reflex was absent and the left was extremely weak, the achilles reflex was absent. There was slight edema, which was quite evident, over the tibia, the face also was somewhat edematous. The hypesthetic zone was somewhat larger than before. The patient complained of a sensation of fullness, loss of appetite, distaste for food and eructation accompanied by nausea and vomiting. At the end of February symptoms of indigestion had become marked, and the intake of food was reduced. His legs were somewhat weak and his gait was unsteady, so that the ascending of stairs was difficult. On February 29, he was unable to walk without support. Hypesthesia had become pronounced in front from the middle of the chest and in back from the middle of the thoracic region downward, including the soles of the feet, these areas were partly anesthetic. Edema of the face and over the tibia was pronounced. On March 4 administration of the vitamin B preparation was begun. The symptoms became ameliorated with the exception of abnormal motility and atrophy. About the middle of March, the heart was distinctly smaller, the area of absolute dullness extended from the midline to the lower edge of the fourth rib and one and one-half fingerbreadths inside the nipple line. Abnormalities of the heart sounds were not present. The patient could take a few steps without being supported. He had regained some strength in his legs, but they were still weak. On March 23 the patient suffered from inflammation of the colon and sigmoid with purulent, mucous and somewhat bloody diarrhea and tenesmus with colicky pain. On May '28 he left the hospital with marked amelioration of symptoms.

The average basal metabolism during the time that the patient was on his usual diet was +1.5 per cent, during vitamin B starvation it was -3.5 per cent, and with vitamin B medication or when the usual diet was resumed, it was +5.0 per cent.

CASES 8 AND 9.—As symptoms did not develop, the protocols of these cases are omitted.

Comparing the protocols of the aforementioned five cases (cases 5 to 9) with the observations of the basal metabolism, we note that in the three cases in which typical symptoms of avitaminosis developed,

TABLE 8—*Metabolism Data on Healthy Patient (Case 8*)*

Date, 1925	Weight in Kg	Body-Surface (Du Bois)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq Meter per Hr	Basal Metabolic Rate (Du Bois)	Temperature, C	Diet and Medication of the Previous Day
1/23	45.2	1.34	58	12	0.67	36.7	-7.1	36.2	Usual diet
1/24	45.2	1.34	58	13	0.81	42.1	+6.6	36.4	Usual diet
1/25	45.6	1.35	56	13	0.76	39.6	+0.2	36.6	Usual diet
1/26	45.3	1.34	54	13	0.75	42.1	+6.6	36.3	Usual diet
2/ 4	46.7	1.36	57	14	0.77	42.4	+7.2	36.6	Restricted diet 7 days
2/13	47.3	1.37	61	12	0.80	43.7	+10.7	36.1	Restricted diet 16 days
2/18	47.3	1.37	62	12	0.72	44.9	+13.7	36.4	Restricted diet 21 days
2/20	47.4	1.37	62	12	0.86	40.6	+2.7	36.1	Restricted diet 23 days
2/23	47.4	1.37	58	12	0.80	43.2	+9.2	36.6	Restricted diet 26 days
2/27	48.2	1.38	62	12	0.83	41.2	+4.3	36.4	Restricted diet 30 days
3/ 3	48.1	1.38	60	11	0.85	40.7	+3.0	36.8	Restricted diet 34 days
3/11	48.8	1.39	71	13	0.80	42.6	+7.9	36.5	Restricted diet 42 days
3/16	48.8	1.39	70	10	0.85	39.8	+0.6	36.4	Restricted diet 47 days
3/20	49.2	1.39	62	11	0.74	42.0	+6.3	36.6	Restricted diet 51 days
3/27	47.6	1.37	72	12	0.83	43.4	+9.8	36.2	Restricted diet 58 days
3/30	50.0	1.40	72	15	0.87	42.9	+8.5	36.5	Restricted diet 61 days
4/ 4	50.4	1.41	68	12	0.80	45.0	+13.9	36.8	Restricted diet 66 days
4/10	51.6	1.41	75	14	0.91	45.2	+14.4	6.1	Restricted diet 72 days
4/13	51.1	1.41	82	14	0.84	41.9	+6.2	36.5	Restricted diet 75 days

* Z. A., man, aged 20, 145.5 cm in height

TABLE 9—*Metabolism Data on Healthy Patient (Case 9*)*

Date, 1925	Weight in Kg	Body-Surface (Du Bois)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq Meter per Hr	Basal Metabolic Rate (Du Bois)	Temperature, C	Diet and Medication
1/28	54.3	1.56	70	15	0.81	38.6	-2.2	36.1	Usual diet
1/29	55.1	1.57	67	13	0.74	44.1	+11.6	35.6	Restricted diet 1 day
1/30	55.3	1.58	65	12	0.72	44.1	+11.6	36.0	Restricted diet 2 days
2/ 6	54.9	1.57	58	12	0.80	39.4	-0.2	35.9	Restricted diet 9 days
2/ 7	55.2	1.57	59	12	0.80	39.8	+0.6	35.9	Restricted diet 10 days
2/13	55.2	1.57	62	12	0.87	40.1	+1.4	35.8	Restricted diet 16 days
2/14	54.7	1.57	62	11	0.72	39.7	+0.4	35.3	Restricted diet 17 days
2/18	55.0	1.57	62	11	0.83	36.7	-7.1	35.4	Restricted diet 21 days
2/20	55.1	1.57	59	12	0.81	38.3	-3.0	35.6	Restricted diet 23 days
2/23	54.6	1.57	59	14	0.79	41.6	+5.3	35.6	Restricted diet 26 days
2/27	55.1	1.57	62	12	0.77	40.2	+1.7	35.9	Restricted diet 30 days
3/ 2	54.5	1.57	56	11	0.82	35.1	-11.1	35.8	Restricted diet 33 days
3/ 6	55.1	1.57	78	13	0.81	41.0	+3.8	36.1	Restricted diet 37 days
3/16	55.0	1.57	63	10	0.83	37.8	-4.3	35.4	Restricted diet 47 days
3/20	54.4	1.57	65	11	0.71	42.7	+7.8	36.2	Restricted diet 51 days
3/23	54.8	1.57	63	12	0.76	40.2	+1.7	35.8	Restricted diet 54 days
3/27	55.2	1.57	68	12	0.72	44.8	+13.4	35.8	Restricted diet 58 days
4/ 4	55.3	1.58	66	11	0.83	37.6	-4.7	35.9	Restricted diet 66 days
4/10	55.6	1.58	72	11	0.86	43.2	+9.3	35.8	Restricted diet 73 days
4/13	55.6	1.58	64	9	0.81	43.7	+10.7	35.8	Restricted diet 76 days
4/17	56.1	1.58	69	12	0.82	39.0	-1.4	35.9	Restricted diet 80 days
4/20	55.9	1.58	66	12	0.74	40.3	+2.0	35.8	Restricted diet 83 days
4/24	55.9	1.58	64	15	0.70	36.3	-8.0	35.9	Restricted diet 87 days
4/30	56.1	1.59	72	13	0.85	41.1	+1.5	35.9	Restricted diet 93 days
5/ 3	55.9	1.58	65	14	0.83	36.6	-7.4	35.8	Restricted diet 96 days
5/ 9	55.9	1.58	57	14	0.80	40.6	+2.8	35.8	Restricted diet 102 days
5/13	55.9	1.58	68	14	0.77	37.1	-6.1	35.8	Restricted diet 106 days
5/18	55.8	1.58	64	16	0.79	33.6	-15.0	36.0	Restricted diet 111 days
5/22	55.4	1.58	64	14	0.79	30.0	-26.5	36.0	Restricted diet 115 days
5/27	55.9	1.58	64	14	0.64	31.2	-21.1	35.9	Restricted diet 120 days
6/ 1	54.5	1.57	68	15	0.76	41.0	+4.1	35.9	Usual diet 2 days
6/ 5	54.9	1.57	59	15	0.73	34.1	-13.8	36.0	Usual diet 6 days

* H. F., man, aged 20, 161.3 cm in height

* From May 7, the restricted diet was boiled twice

there was more or less decrease in the basal metabolism (the average decrease during the avitaminous alimentation being 12.1 per cent, 9.4 per cent and 5 per cent), while in two cases, in which observations were made for a long time and in which no symptoms developed, there was no change in the basal metabolism except during the last period in the last case (case 9), after administration of twice boiled accessory food, serious distaste for the food and indigestion occurred, and the intake of food was highly reduced. Especially interesting is case 5, in which the prescribed food was always eaten until the end of the experiment. The basal metabolism in this case had been typically reduced, remarkably at the beginning of the development of the symptoms and rising somewhat during the latter period, parallel with the increase in the pulse rate. Vitamin B medication caused increased metabolism. In case 6 a low rate of metabolism still continued after administration of the vitamin B preparation. It is difficult to explain this, we shall only mention that the intake of food, especially on the previous day of determination of the basal metabolism, was sufficient, although the patient had not recovered his appetite, and a slight paralysis of the legs was present (when paralysis exists, increase in the basal metabolism is usually postponed). After the administration of the vitamin B, however, the basal metabolism gradually returned to the original value, with amelioration of the symptoms. In case 7 there was also a slight decrease in the basal metabolism with the beginning of the symptoms but the change in this case was not so remarkable as in other cases, perhaps because an increase in the pulse rate appeared relatively early. After resuming the usual diet, the basal metabolism again became increased (the average pulse rate at the time of determination of the basal metabolism during vitamin B starvation was 62 in case 5, 60 in case 6 and 78 in case 7).

COMMENT

The first series of experiments showed that vitamin B starvation causes an aggravation of symptoms of beriberi and a marked decrease in the rate of basal metabolism. After administration of a vitamin B preparation, the symptoms were ameliorated, and the basal metabolism resumed its original value. The second series of experiments showed that by means of a long continued diet deficient in vitamin B, typical symptoms of avitaminosis develop, and the rate of basal metabolism decreases, especially at the initial symptoms, increasing somewhat with the involvement of the cardiovascular system (increase of the pulse). The decrease in basal metabolism in the second series was not so remarkable as in the first series of experiments, which probably is due to the degree of the deficiency of vitamin B in the diet. If the deficiency of vitamin B is slight, no symptoms develop, and the basal metabolism

shows almost no change, as in cases 8 and 9. From these results it may be concluded that vitamin B starvation without general starvation causes a decrease in the basal metabolism, in beriberi it causes an aggravation of the disease, in healthy persons typical symptoms of avitaminosis develop after an incubation. The decrease in the basal metabolism is especially significant just at the beginning of the symptoms, becoming less significant later, parallel with the increase in the pulse rate. In both series the symptoms are ameliorated after the administration of vitamin B. From these observations it seems plausible that the deficiency in vitamin B has some special relation to the exacerbation or aggravation of beriberi.

It seems important to consider whether beriberi and avitaminosis are one and the same disease or two different diseases with some similar symptoms. This problem has already been enthusiastically discussed by many investigators, but is not yet definitely solved. We have not tried to survey the literature for a solution to this problem, as results are too numerous and contradictory and too far from our main purpose. We found that in beriberi the basal metabolic rate is usually normal, and when cardiovascular involvement becomes significant, it is increased, when paralysis occurs the rate decreased. Our experiments show that there is a definite decrease in basal metabolism in the course of vitamin B starvation, so that it seems probable at first that beriberi and avitaminosis are essentially two different diseases. However, the decrease in basal metabolism during vitamin B starvation is especially significant at an early period of avitaminous manifestation followed by an increase nearly parallel with the increase in the pulse rate. In view of the fact that most investigators never recognized the resemblance of the remarkable cardiovascular symptoms in avitaminosis to those in beriberi until now, the difference in observations in the basal metabolism must be used cautiously in the differentiation of these two diseases. Observations on the basal metabolism by some of the leading research workers on beriberi in Japan have shown that there are still many factors in these two diseases which are different, therefore we cannot yet say definitely whether beriberi and avitaminosis are two diseases or the same disease. It is possible also that in addition to the avitaminous state some other important factor is necessary to account for the manifestation of true beriberi.

SUMMARY AND CONCLUSIONS

1. Vitamin B starvation in patients with beriberi causes aggravation of the symptoms and a decrease in the basal metabolism. Administration of a vitamin B preparation ameliorates the symptoms and increases the rate of basal metabolism.

2 Prolonged vitamin B insufficiency in healthy persons causes typical avitaminosis and decrease in the rate of basal metabolism, especially at the beginning of the manifestation of symptoms. Administration of a vitamin B preparation cures the symptoms and increases the rate of basal metabolism.

3 The identification of beriberi with avitaminosis is difficult at present as there are many factors in these two diseases which are not similar. According to the observations on the basal metabolism, the diseases do not coincide. In beriberi we usually found that the basal metabolism was normal. When decompensation was threatened, there was an increase in the rate, and when paralysis and atrophy were present, there was a decrease. In avitaminosis we always found a decrease in the basal metabolism, especially at the beginning of the exacerbation of the symptoms. A serious involvement of the cardiovascular system in avitaminosis which possibly causes an elevation of the rate of basal metabolism was not observed. We know that when the pulse rate increases in the course of avitaminosis, an increase in the rate of basal metabolism follows. Therefore it is difficult to decide without further investigation whether or not this divergence in the metabolic observations has an essential value for the differentiation of these two diseases.

(The clinical observation and other investigations of the avitaminosis experiment were performed by Professor Inada, Drs. Mozai, Tanino, Akiya, Horiuchi, Ohta and Donomae.)

EXOPHTHALMIC GOITER AND THE INVOLUNTARY NERVOUS SYSTEM

XIII THE COURSE OF THE SUBJECTIVE AND OBJECTIVE MANIFESTATIONS OF EXOPHTHALMIC GOITER IN FIFTY UNSELECTED PATIENTS OBSERVATIONS FOR FIVE YEARS WITHOUT INSTITUTION OF "SPECIFIC" THERAPEUTIC MEASURES ("SPONTANEOUS COURSE")*

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In a previous article¹ on exophthalmic goiter and the involuntary nervous system, we have recorded our observations on fifty unselected patients studied for two years. The following excerpt taken from this article will explain the system we followed in making our observations.

In January, 1921, we instituted a study of fifty unselected cases of fully developed exophthalmic goiter. No specific therapeutic measures were employed "in order to determine the natural history (spontaneous course) of the disease,"² and to establish an "index for the evaluation of therapeutic procedures."³ From the group were excluded (a) patients who had thyroid enlargement without other manifestations of exophthalmic goiter,⁴ and (b) those who, with or without thyroid enlargement, presented sympathomimetic symptoms, without significant elevation of the basal metabolism (autonomic imbalance).⁵ In the group studied, we included (1) patients with a significant elevation of metabolism on repeated readings, (2) patients whose illness was sufficiently severe to warrant residence in a hospital where beds are at a great premium (two exceptions), and (3) patients from the poorest sections of the city, who were subjected to constant economic strain (one exception).

The patients were first observed in the general wards of the hospital. An attempt was made to secure for them complete physical and mental relaxation. A high caloric diet (3,000 calories) was ordered and wet packs at 75 degrees were used daily. In the beginning, daily colon irrigations were employed, but these were later discontinued. Foci of infection, particularly in the nose and

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1 Hyman, H. T., and Kessel, Leo. A Study of Exophthalmic Goiter and the Involuntary Nervous System, *Arch Surg* 8:149 (Jan) 1924.

2 Kessel, Leo, Hyman, H. T., and Lande, Herman. A Study of Fifty Consecutive Cases of Exophthalmic Goiter, *Arch Int Med* 31:433 (March) 1923.

3 Lieb, C. C., Kessel, Leo, and Hyman, H. T. *Am J M Sc* 165:384 (March) 1923.

4 Kessel, Leo, Hyman, H. T., and Lieb, C. C. Exophthalmic Goiter and Involuntary Nervous System, Clinical and Laboratory Study of Involuntary Nervous System, *JAMA* 79:1213 (Oct 7) 1922.

5 Kessel, Leo and Hyman, H. T. *Am J M Sc* 165:387 (March) 1923.

6 Kessel, Leo and Hyman, H. T. *Am J M Sc* 165:513 (April) 1923.

throat were attacked, and extirpated or drained Phenobarbital (luminal), $1\frac{1}{2}$ grains, was used as a hypnotic and syrup of ferrous iodid, from 5 to 30 minims, three times a day, was prescribed to hasten the involution of the thyroid.

After an average hospital stay of six weeks, the patients were sent to the country, and were given small tasks. In another two to six weeks, they were returned home, and permitted to resume their responsibilities gradually. They were instructed as to their disease and were warned that the condition was arrested rather than cured and the possibility of recurrence was emphasized. They were urged, in addition to regular attendance at the out-patient department, to return at the recurrence of the slightest symptoms. The families were warned that these people must be protected, but without coddling. All the follow-up observations were made personally by us. In our presentation, we included a history of these fifty consecutive patients, irrespective of end-results, and with extensive follow-up observations. When the patient could not be kept under observation, we regarded the issue as unsuccessful.

In this paper, we present the subjective and objective results at the conclusion of a period averaging fifty-eight months, including all data to Jan 1, 1927.

SUBGROUPING OF PATIENTS

A Fatalities—Eight deaths have occurred, of which one, due to a carcinoma of the stomach, is excluded from the statistical study. The remaining seven deaths may be summarized as follows: cardiac failure, two, infection, one, status lymphaticus, one, thyrotoxicosis, two, and thyroidectomy, one. Five of these deaths have been discussed previously.⁶ Since this report was made, two patients, elderly women, have died of cardiac failure due to exophthalmic goiter. In addition, one had severe diabetes mellitus, and the other a superimposed subacute bacterial endocarditis. They would have been desperate operative risks even when first admitted to our service.

B Patients Who Sought Specific Therapy—Ten patients considered their progress unsatisfactory, and sought some type of specific therapy. We regard these as "failures" from our standpoint. One patient (B A V) received treatment from an endocrinologist. We have been unable to obtain complete records from her or from her physician. Another, (D H) received radium therapy, with what appears to be an excellent result. This is the only noteworthy result of radium therapy that we have observed.

7 "1 Almost without exception, no patient in this series received iodid during the first month of observation and rarely within the first six weeks, during which time the greatest improvements were noted. 2 The administration of the iodids was not accompanied by any marked alteration in the rate of improvement in our experience when benefit accompanied the exhibition of the drug, it was unusual to observe any changes other than a continuation of the amelioration of symptoms noted in the preceding weeks." There was no other routine medication. No purposeful psychotherapy was employed, but the patients were shielded, as far as possible, from psychic trauma, and attempts were made to adjust their social and economic difficulties.

The remaining eight patients were subjected to a subtotal thyroidectomy, either at our institution or elsewhere, and we have fortunately been able to follow most of them throughout their course.

One man (M F referred to in section A) died immediately following operation. The operative mortality in this group is therefore 12.5 per cent.

One patient (D J) made good progress. We had observed her for two years of relatively uncomplicated convalescence, and then, following an automobile accident, an exacerbation ensued. When the patient was treated with a compound solution of iodine and rested in bed, the basal metabolic rate fell from plus 65 to plus 24 per cent. Dr Moschowitz then performed a subtotal thyroidectomy, which was followed by a severe and prolonged postoperative reaction. The patient was discharged on the fifteenth day after operation, with a normal basal metabolic rate, and in the two years that have elapsed she has gained 34 pounds (15.4 Kg). Though she has gone through a pregnancy, the basal metabolic rate and the pulse rate are normal. The exophthalmos is unchanged.

We regard the results in three cases as good, but not particularly brilliant. One of these patients (R B) was given roentgen-ray therapy at the Roosevelt Hospital, and then a ligation was performed in October, 1922. At a second admission, two months later, a partial thyroidectomy was performed, with a resultant fall in the basal metabolic rate from plus 43 to plus 6 per cent, and a gain of 21 pounds (9.5 Kg). At the third admission, in October, 1924, another partial thyroidectomy was performed, following which the patient was admitted to the Memorial Hospital where a diagnosis of carcinoma of the parotid was made by Dr Coley. Six months later, however we heard that the patient was doing fairly well. We have not been able to complete our records in this case. Another patient (B R) has been relieved of attacks of paroxysmal cardiac irregularity since thyroidectomy was performed, though the operation was followed by aphonia from paralysis of the cord. Finally, a young girl (G D) was observed by us for thirty months, and then had a partial thyroidectomy performed by Dr Emil Goetsch in October, 1923, after four roentgen-ray treatments. The basal metabolic rate before operation was only minus 3 per cent. The patient was in the hospital for ten days and most of the right lobe and isthmus were removed. She has as residual symptoms a tachycardia of 100, an exophthalmos of 23-23, and hyperplasia of the thyroid remnant, but she is considerably better than at any time prior to operation, and able to fill a difficult position.

Three operative results are indeterminate. One woman (M H) was symptom-free at the time of operation. Another woman (N J), after a stormy period under our care, had a ligation performed by

Dr Cile in August, 1923, which was followed by a severe reaction. A second ligation was performed on September 2, and two months later a subtotal thyroidectomy, this was followed by dysphonia from paralysis of the cord. For the next eight months her nervousness, irritability, asthenia, palpitation and tremor were unimproved, and at rest she had a pulse rate of 116. She went home to New Zealand, improving considerably during the ocean trip, and when we saw her two years after operation, she was much better but by no means well. One patient (L R) had a partial thyroidectomy performed by Dr John Erdmann in June, 1923. Eight months later she was improved but still complained of nervousness, tremor and palpitation. Her exophthalmos measured 20-20, the thyroid remnant had undergone a compensatory hyperplasia, she had a tremor and a pulse rate during examination of 136. Nine months after this, she was considerably improved. Her basal metabolic rate was normal, and for another six months her progress was satisfactory. Then she had a recurrence of an old sinus infection, which resulted in an exacerbation of symptoms, and she went to Dr Cile, who completed the thyroidectomy in September 1926. We saw her two months following operation and, while she was still weak, she was somewhat improved, her pulse rate was 78, and she had gained 10 pounds (4.5 Kg). The exophthalmos was unchanged. It is too soon to estimate the value of the operative procedure.

In addition to these eight, six of our patients had had operative treatment before they came to us. In every one of these six instances, the symptoms had recurred with sufficient intensity to incapacitate the patient. Of the six, one (L K) died of a status lymphaticus fourteen years after subtotal thyroidectomy was performed. Partial thyroidectomy was performed on three patients and simple ligations on two, with unfavorable results.

C Patients Lost from Observation—Three patients were lost from observation. Two were doing poorly when we last saw them (E N and S S). One man (J W) was doing well when last seen.

D Patients Successfully Followed—Thirty-one patients have been successfully followed, twenty-five for more than four and a half years and fourteen for over five years. We shall analyze the progress of these thirty-one persons.

1 *Subjective Symptoms*—It is difficult to present and interpret the subjective symptoms of patients with exophthalmic goiter. A few generalizations can be made. The subjective symptoms did not entirely disappear in any of our patients. The subjective symptoms do not bear a constant relation to the intensity of the disease, to the basal metabolic rate or to the economic restitution of the patient. Asthenia,

nervousness, insomnia and palpitation are symptoms particularly prone to persist or to recur on slight provocation. Economic restitution is by no means analogous to freedom from subjective complaints. As a general rule, however, it is fair to say that the subjective symptoms in these patients have strikingly and markedly diminished.

2 Objective Observations (a) Exophthalmos The right hand columns in chart 3 indicate the first and the last exophthalmometer readings. The last reading averages five years after the first. Thirteen of the twenty-four completed records do not show appreciable change. Seven have decreased slightly, and four have increased. The other eye signs in exophthalmic goiter are subject to individual variation, and are lacking in value because such signs as von Graefe's, particularly, may be observed in persons without exophthalmic goiter. We urge exophthalmometer readings as a routine measure, for they are the only accurate gauge of the eye signs.

(b) Pulse Rate The pulse readings obtained in a follow-up clinic are subject to so many modifications that they are impossible to interpret with any degree of accuracy, and our observations on pulse rate are therefore of little value. The basal pulse should be recorded in exophthalmic goiter, and usually parallels the basal metabolic rate. In order to obtain the basal pulse rate, the same elaborate precautions which are necessary in estimating the basal metabolic rate should be exercised, and this we have not been able to do in a follow-up clinic. Therefore, we prefer to omit our observations on the pulse rate, rather than to report grossly inaccurate figures. All of our patients retained a lability of the pulse rate, and it was exceptional to record a rate of below 80, even when the basal metabolic rate was normal and the patient symptom-free.

(c) Tremor Many of these patients retain a fine tremor, visible only on examination of the outstretched fingers. In no instance was the tremor complained of subjectively or was it of sufficient intensity to interfere with the patient's occupation.

(d) Goiter In no instance did the goiter completely disappear, though in four patients it was noticeable only to the examiner. Any attempt to classify these patients according to the anatomic appearance of the goiter was unsuccessful. While patients could be distinctly classified clinically, as has been pointed out by many writers,⁸ this classification could not be correlated with the alterations in the thyroid gland.⁹ In presenting another group of patients, in which the opportunity of making histologic studies was afforded, this point will be dealt with more fully.

⁸ Plummer, H. *Tr. A. Am. Phys.* 1916, p. 138.

⁹ Graham, Allen. *Exophthalmic Goiter and Toxic Adenoma*, *J. A. M. A.* 87: 628, (Aug. 28) 1926.

(c) Basal Metabolic Rate¹⁰ The course of the basal metabolic rate is recorded graphically in chart 2, and the individual records appear in chart 1. In chart 1 the first line of figures represents the basal metabolic rate on admission, and at six and twelve months are recorded the readings which occurred nearest to that period. Naturally, many readings were made in the first few weeks, during the course of the hospital stay, and all of these are omitted from this chart, but they appear in a previous paper.¹ After the twelfth month all the readings are recorded, for these have not hitherto appeared, and they give an excellent idea of the progress of the patient.

From chart 2 it will be seen that at the end of six months the average basal metabolic rate, which on admission was plus 43 per cent, had fallen to plus 22 per cent, and at the twelfth month to plus 17 per cent. The fall continues at two and three years to plus 14 and plus 10 per cent.

In the fourth year, there is a slight rise, due to four high readings that occurred in the patients. In the forty-eighth month, in patient 1, a basal metabolic rate of plus 39 per cent is recorded, following a serious accident to her son. In patient 9, also at the forty-eighth month, a basal metabolic rate of plus 50 per cent is recorded, as a result of a purulent pansinusitis. In patient 22, two high readings are recorded, of plus 34 per cent and plus 53 per cent, and these occurred while the patient was gaining 40 pounds (18.1 Kg.) over her weight on admission. She is an extremely stupid person, and we have never been able to secure her cooperation during the basal metabolism test. We are therefore more inclined to believe that this reading is not basal.¹¹ But one other reading of over plus 17 per cent occurred, and the average of the remaining readings is plus 8 per cent.

In the fifth and sixth years slight rises are observed, the average being plus 17 per cent in the fifth year, and plus 19 per cent in the sixth year. These rises again are due to individual elevations. Thus, plus 49 per cent in the third patient on the list was recorded during an attack of paroxysmal flutter just prior to her marriage. Sixteen months later, her basal metabolic rate was found to be plus 12 per cent. Again, in patient 5, a plus 40 per cent is recorded in the sixty-third month, at a time when her husband was out of work, and she was suffering great privation and was overworking. During this period, and

10 The readings of the basal metabolic rate have been made on the Roth-Collins machine by Dr. Herman Lande and his assistant, Miss A. K. Steiner.

11 Since the writing of this article, we were fortunately able to secure another basal metabolic rate on this patient on Jan. 18, 1927, when, with adequate cooperation from the patient, her rate was recorded at plus 17 per cent.

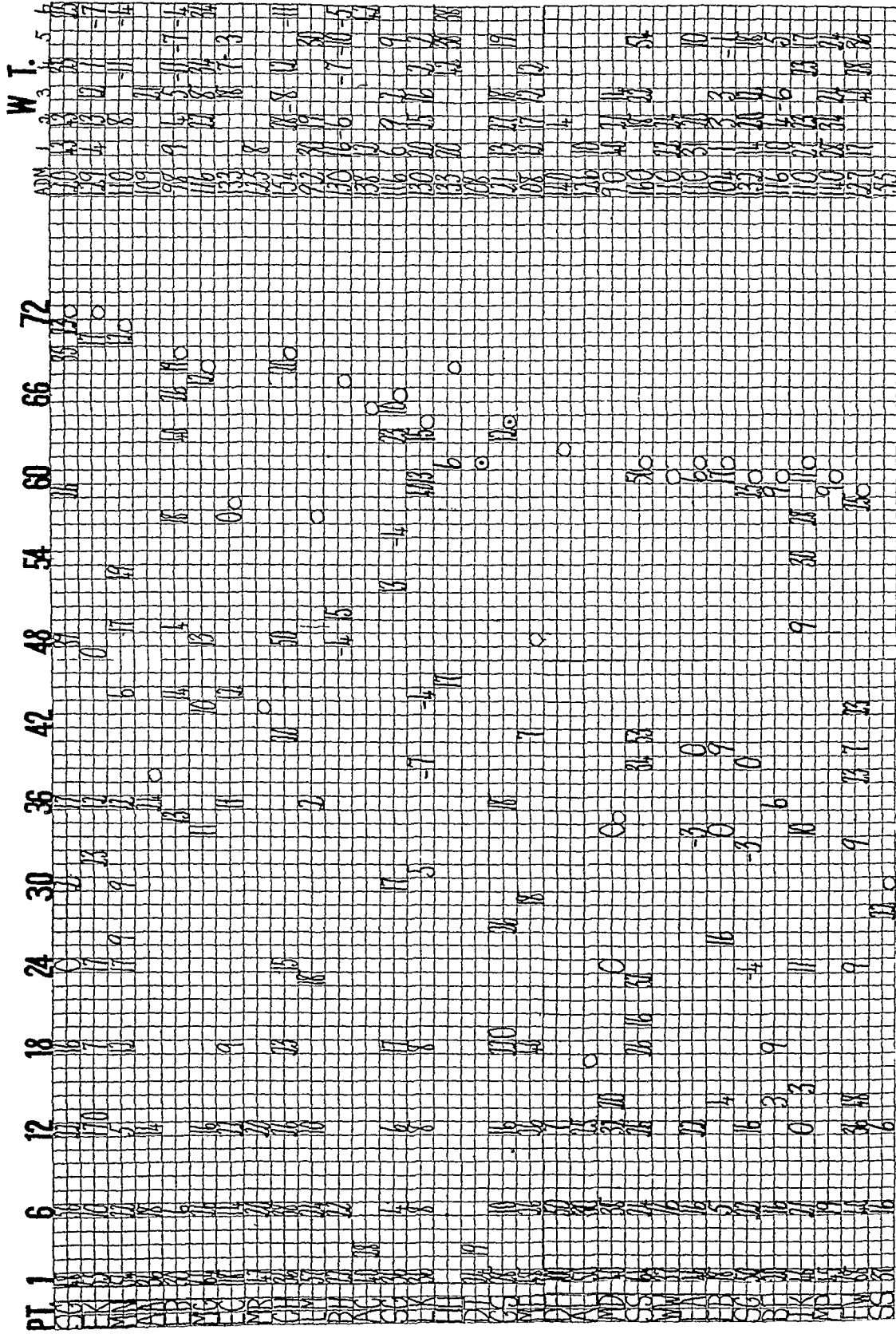


Chart 1—The individual record of the basal metabolic rate and weight throughout the course of observation. The first figure gives the basal metabolic rate on entrance. The figure at six months is the nearest reading to that time. All the intermediate readings are omitted, but appear in article X (Arch Surg 8:149 [Jan] 1924). After the sixth month all readings are included. The dot with the circle around it indicates the time of the last visit. The weights at the various years are given in reference to the weight at admission and are not cumulative.

despite the elevation of her basal metabolic rate, she was working from 6 in the morning until between 10 and 11 at night, as janitress in a tenement house, in addition to taking care of her household. In the sixty-eighth month, her rate had fallen to a plus 19 per cent. During this period, she was not at any time economically incapacitated. Again, a plus 40 per cent is recorded in the fourteenth patient in the fifty-ninth month. This occurred simultaneously with a miscarriage, and a month later, following a curetage, the rate fell to plus 13 per cent. A rate of plus 50 per cent is recorded in patient 22, to whom reference has already been made. If these readings are omitted, the average reading would have been 13 per cent in the fifth year and 17 per cent in the sixth year.

It should be understood that all readings were taken while the patients were ambulatory, so that they are, if anything, slightly higher than would be obtained in patients who were in bed. Many of our patients who were progressing satisfactorily could not leave their work to come to the hospital for metabolic readings. An example of this is patient 10, who had a rate of minus 2 per cent in her thirty-sixth month and who, owing to her work, was unable to report for a basal metabolic reading thereafter.¹² A reading has not been made for patient 16 since her third month. This patient lives out of town, and we hear from her only by letter. Patient 19, who had a basal metabolic rate of plus 7 per cent at one year, has not been able to come for a reading since, though we are still in communication with her at the sixty-second month. She has just had another baby, and cannot leave it to come to the hospital. Patient 23, whose last reading was a plus 16 per cent in the sixth month, lives out of town, and writes to us that he does not have any symptoms referable to exophthalmic goiter. Had these patients been able to call on us, the average basal metabolic rate would have been materially lowered.

The basal metabolic rate that reached normal in the twelfth month, has remained well within normal limits throughout the following five years.

Nineteen readings of zero or an actual minus will be seen, contrary to the usual statement that these patients do not reach normal or subnormal readings unless they are the subjects of specific therapy. None of these patients presented any clinical evidences of myxedema.

(f) *Weight* The weights are recorded in chart 1. The graphic chart shows an increase of 18 pounds (8.2 Kg.) in the first and second year, and, though this gain was not completely held in the succeeding years, the patients did maintain an average gain of 11, 12 and 13 pounds

¹² Since the writing of this article, the patient has reported for observation and her basal metabolic rate is plus 4 per cent in the fifty-ninth month.

(5, 54 and 59 Kg) in the third, fourth and fifth years, respectively. The record of the weight of each patient will be seen to the right of chart 1, the first column being the weight on admission, and the readings in the other columns show the loss or gain during the various years. Loss of weight is indicated with a minus sign, if no sign occurs, there is a gain. These figures are not cumulative, but each figure is with reference to the admission weight in the left hand column.

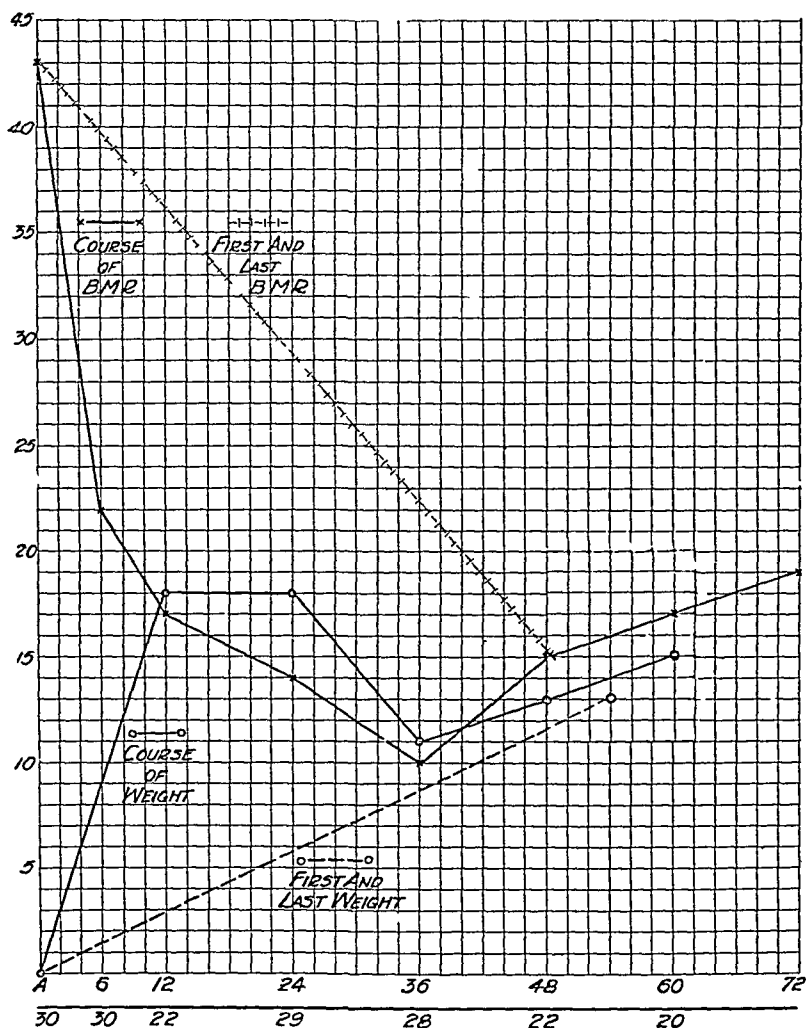


Chart 2—The course of the weight and basal metabolic rate in exophthalmic goiter. The first and last basal metabolic rate and weights are compiled from the entrance figures and the last figures available, and the time is the average of the last observations. The course of the weight and basal metabolic rate is based on all available readings after the sixth month, and the figures at the bottom indicate the number of readings on which the final readings were based. The individual readings will be seen on chart 1.

A few comments on the patients may be of more than passing interest. In the first year, nine patients gained 20 pounds (9 Kg) or more. In only one patient has a loss of weight occurred in the first two years. In the third year, two losses in weight occurred, one in the

same patient in whom it occurred during the second year. At the end of six years, six patients show a loss in weight, and twenty-five have gained weight, the average difference in weight between the first and last weight being 14 pounds (6.4 Kg). One patient has gained over 50 pounds (22.7 Kg), and this patient, curiously enough, is the one who had a plus 50 per cent metabolism in her sixtieth month and a plus 53 per cent in her forty-first month, we have commented already on this patient. Five patients have gained 30 pounds (13.6 Kg) or more, and four more between 20 and 30 pounds, so that ten of the twenty-six patients have gained more than 20 pounds in the course of the six years.

Of the six who lost weight, one has lost 1 pound (0.5 Kg), one 5 pounds (2.3 Kg), one, 7 pounds (3.2 Kg), and two have lost 4 pounds (1.8 Kg). One woman has lost 11 pounds, she is the patient with the recurrent pansinusitis.

(g) Social and Economic Restitution. Social and economic restitution is the most important desideratum from the standpoint of the patient, and may be independent of any of the subjective and objective manifestations. In this group (chart 3), there is an average period of hospitalization (full shading) of six weeks and an average period of rest in the country (three-fourths shading) of five weeks, which is followed by variable periods of rest at home (half shading). By the third month fifteen or over half, were restored, by the sixth month, all but three patients were economically restored. Of the three patients who had a prolonged convalescence, one (A. C.) was a malingerer and another (A. L.) was an old woman with essentially abdominal symptoms, due to a cholecystitis. The third was a young girl (M. D.), who, despite the prolonged period of convalescence, has made favorable progress since. During the remainder of the period of observation, little or no economic and social incapacitation has occurred, as will be seen by an almost complete absence of shaded portions. Eight periods of incapacitation, due to some disease other than exophthalmic goiter (hatching), have occurred. In most instances these were due to a tonsillectomy (*T*) or to an infection of the upper respiratory tract (*I*). In only one instance did a true exacerbation occur, in the third patient's fifty-third month, a mild exacerbation developed and was accompanied by a paroxysmal flutter prior to marriage.

Worthy of comment, too, is the number of pregnancies that have occurred. Eight of the patients have borne twelve normal children, without exacerbation of symptoms, and the pregnancy, labor and children have all been normal. The test of labor was adequately met in all instances.¹³

13 The majority of these patients were delivered by Dr. C. F. Jellinghaus at the Lying-In Hospital in New York.

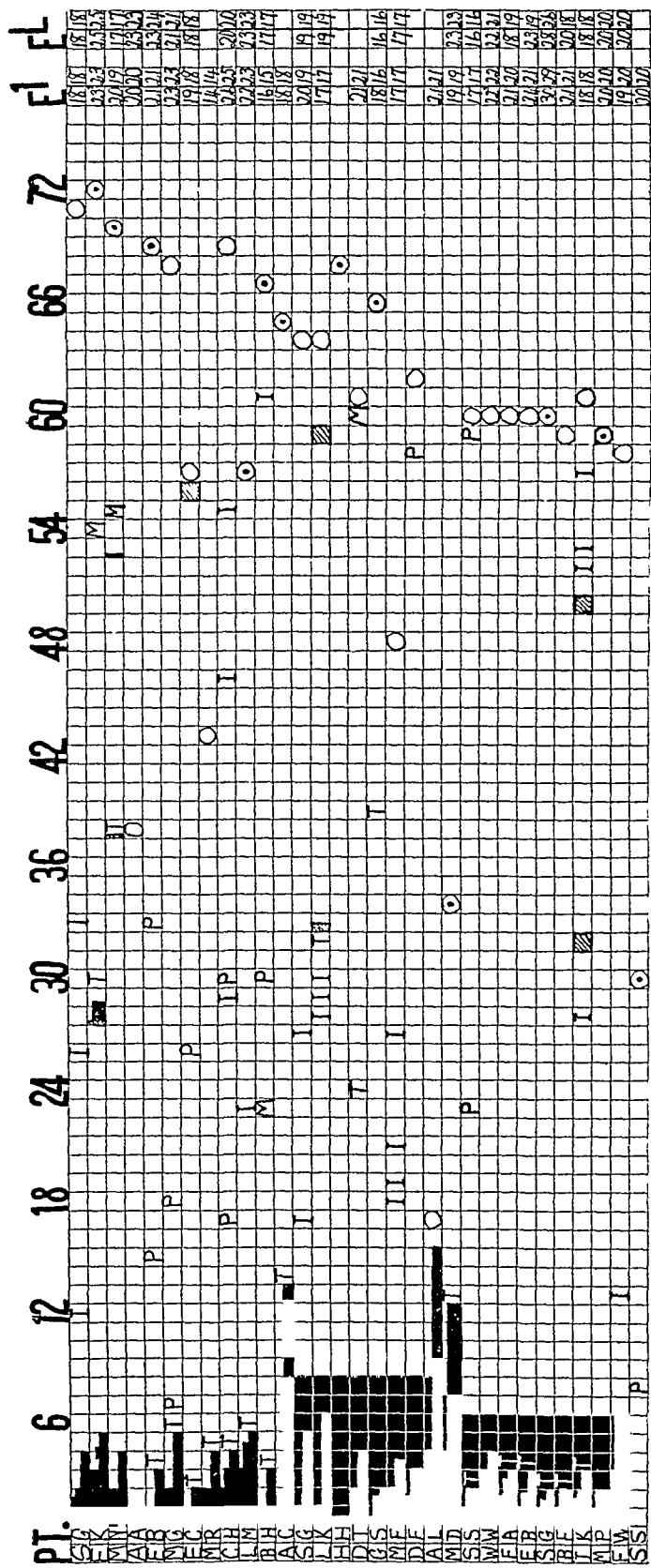


Chart 3—The course of the disease with regard to social and economic incapacitation. The patients are listed in the same order as in chart 1. Full shading indicates hospitalization, three-quarter shading, rest in the country, half shading, rest at home, hatching indicates incapacitation due to some disease other than exophthalmic goiter. When no shading occurs, the patient is socially and economically restored. *I* indicates infection, usually of all the upper respiratory tract, *T*, tonsillectomy, *P*, pregnancy, *M*, marriage. The time of the last observation is again indicated by a dot with a circle around it. The exophthalmometer readings are the first and last for each eye.

Economic restitution occurred for an average of fifty-two months in the fifty-seven months' average span of observation in this group. The average time for social and economic restitution was four and a half months and during the remaining fifty-two and a half months these people were able to assume their burden as wage-earners or housewives in the trying circumstances of metropolitan life. They all had residual symptoms, usually negligible, sometimes annoying but never sufficient to cause them to go to bed, partially due to the fact that a day or even a few hours in bed among this class of patients is far too great a luxury. Doubtless the same symptoms in the more leisurely walks of life would have resulted in variable periods of incapacitation. At times the recurrence of the symptoms was associated with elevation of the basal metabolic rate and loss of weight, but in only one instance was this sufficient to compel the patient to seek hospitalization.

It would be wrong to give the impression that this period was as free from difficulty as the chart would make it appear. Difficulties and symptoms of one type or another were constantly present, but the important fact is that none of these difficulties or symptoms were sufficient to result in the patient's being economically incapacitated.

(h) *Complications and Associated Diseases* Among the associated conditions the most common were tonsillar and upper respiratory infections. Both of these bear an etiologic relationship to the disease, as we have previously indicated.¹ Tonsillectomy was performed on twenty-four of the patients—on ten under local and on fourteen under general anesthesia. We observed no unusual reactions to the tonsillectomy, except that in one instance a patient suffered a severe and prolonged sympathomimetic sensitization from the procaine hydrochloride. The choice of anesthesia is still a matter for discussion.

A number of patients suffered from intercurrent and unassociated conditions, such as chronic bronchitis, gynecologic disturbances, cholelithiasis, asthma and infectious arthritis.

The alleged degenerative changes have not occurred in these patients with any degree of regularity. Two men have hypertension, and have had it all these years without alteration in the heart or kidneys. We are under the impression that the hypertension is more apparent than real, and varies in these patients with the same lability as the pulse rate. Three women have had attacks of cardiac irregularity on provocation, in all, the irregularity has subsided and has not recurred.

(i) *Subgroupings* The clinical picture of exophthalmic goiter is rarely typical, and generally no two patients present the identical syndrome. Two large subdivisions are clearly to be noted, as was first pointed out by Plummer. These subdivisions are characterized most

clearly by the exophthalmos in the one group and by little or no exophthalmos in the other. Usually, the group without exophthalmos are older and the symptoms are of longer duration, more often there are cardiac symptoms. We clearly recognize these subdivisions, but that the differences in the two groups are due to any histologic alteration in the thyroid, such as the presence or absence of adenomas, or to any alleged change in the secretion of the thyroid, seems to us to be an unwarranted conclusion, for reasons to be discussed more completely in another place. Of our thirty-one patients here listed, twenty-four would be included in the exophthalmic group and seven in the nonexophthalmic group, of the remaining nineteen patients, seven would be included in the nonexophthalmic group and of these four died. The percentage of deaths in the nonexophthalmic group is therefore considerably higher than in the other group, so that these patients are clearly more liable to cardiac complications, infections and fatal thyrotoxicoses. The explanation for this, to us at least, is not patent. Of the patients who sought specific therapy, nine were in the exophthalmic group, and of those lost from observation, one was in the exophthalmic group, so that in the nonfatal cases which we regard as failures, three were in the nonexophthalmic group and ten in the exophthalmic group. From this small series of observations we can simply say that if the two subdivisions are recognized, patients in the nonexophthalmic group are seen less frequently, are more prone to fatal or incapacitating complications, and usually are older women. The fact that these people have adenomas in their gland by no means proves that the adenomas are the cause of the alteration in the clinical picture, for they may occur much more commonly in patients without symptoms, they may also occur in patients with the exophthalmic type of the disease or in myxedema. This attempt to classify clinical material on pathologic changes in the thyroid suffers from the same weakness as the now neglected theory that pathologic hyperplasia of the thyroid is indicative of a physiologic hypersecretion, a theory as strongly urged and with as little actual demonstration as the present theory of the toxicity of adenomas.

SUMMARY

The facts concerning the spontaneous course of exophthalmic goiter are presented baldly, with a minimum of comment, and without effort to evaluate specific methods of therapy. This presentation is made for the purpose of establishing a norm or control, and not for the purpose of outlining a therapeutic policy. Later we shall report our results with various types of specific therapy, and, having so done, we shall make an attempt to discuss therapeutic policies. Our purpose is the collection of data, and not an attempt to prove or disprove theories or points of view. Of the fifty patients, the spontaneous course was followed in thirty-one, of the nineteen whose spontaneous course could not be completed, six

died (a mortality of 12 per cent) and thirteen were either lost from observation or received specific therapy. Of the latter, two received nonoperative therapy, and eight operative therapy, one of the eight died, making operative mortality in this group of 12.5 per cent.

With regard to the spontaneous course, we may conclude that in considerably more than half of the patients economic and social restitution may be expected after the fourth month and will continue up to at least on an average of fifty-seven months, and that this restitution is made in the presence of residual symptoms and despite the stress and strain of the needy in a metropolitan district.

BLOOD GROUPS IN TUBERCULOSIS [†]

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OLIVE M SEARLE, M S

AND

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Recently added emphasis has been given to the importance of the constitutional factor in disease through the work of Draper,¹ Kretschmer² and others. The work of these men has been based largely on structural or morphologic observations. It was felt that an approach to this problem from the standpoint of the basic physiologic pattern, as suggested by Draper, might also prove of interest.

With this in view, a study of the distribution of the blood grouping was made in a series of tuberculous subjects, blood type being generally regarded as an outstanding constitutional quality, and tuberculosis as representing a somatic disorder of traditionally important genotypic relationship. The only previous work appearing in the literature is that of Alexander,³ who studied fifty cases with apparently negative results. Obviously, however, such a series is too small to warrant a valid conclusion.

The series utilized in this study was comprised of 400 cases, all but 12 of which were of the pulmonary type. The subjects were of both sexes and were racially distributed as indicated in table 1. Three hundred and fifty-two, or 88 per cent of this series, fall into the so-termed "European" group,⁴ for which an apparently adequate norm has been established.

The actual typing was carried out essentially according to the simplified technic of Moss,⁵ using known serums of groups II and III and the cells of the unknown subjects. The grouping of the blood specimens used for the known serums was checked by cross-agglutina-

[†] From the State Psychopathic Hospital.

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2 Kretschmer, E. Körperbau u. Charakter, Berlin, Springer, 1921.

3 Alexander, W. An Inquiry Into the Distribution of the Blood Groups in Patients Suffering from "Malignant Disease," Brit J Exper Path **2** 66 (April) 1921.

4 Ottenberg, R. A Classification of Human Races Based on Geographic Distribution of the Blood Groups, J A M A **84** 1393 (May 9) 1925.

5 Moss, W. L. A Simplified Method for Determining the Isoagglutinin Group in the Selection of Donors for Blood Transfusion, J A M A **68** 1905 (June 23) 1917.

tion tests of both cells and serum with other blood specimens of known type, and the serums were always used fresh and undiluted. The cells to be tested were obtained by mixing a few drops of blood from a pricked finger with physiologic sodium chloride. A microscopic slide was divided into two sections by a wax pencil mark, a drop of group II serum was placed on one end and a drop of group III serum on the other. A drop of the cell suspension to be tested was added to each serum and thoroughly mixed. The slides were allowed to stand at room temperature and the cell suspension and serum were mixed frequently and examined macroscopically and microscopically for at least twenty minutes. The blood specimens were grouped according to the classification of Moss.

TABLE 1—*Racial Distribution*

Nationality	Tuberculous Subjects	
	Number of Cases	Percentage of Total
German	81	20.25
Polish	43	10.75
Irish	41	10.25
English	38	9.50
French	15	3.75
Scandinavian	12	3.00
Scotch	11	2.75
Finnish	8	2.00
Italian	7	1.75
Negro	7	1.75
Hungarian	7	1.75
Dutch	7	1.75
Austrian	5	1.25
Hebrew	5	1.25
Mixed	92	23.00
Miscellaneous*	21	5.25

* Lithuanian, Russian, Bulgarian, Roumanian, Serbian, Swiss, Armenian, Croatian, Bohemian, Spanish, Slavic.

The results obtained have been tabulated in table 2. It will be seen from this table and from the chart that the distribution found in the total series conforms well with that of the general average of American workers⁶ based on 9,600 cases. Likewise the "European" tuberculous formula seems to show no essential variation from the "European" average or normal pattern, although as compared with both average groups, the number of tuberculous subjects seems slightly low in representation in group I. Whether this observation, however, can be accorded any valid significance is highly speculative.

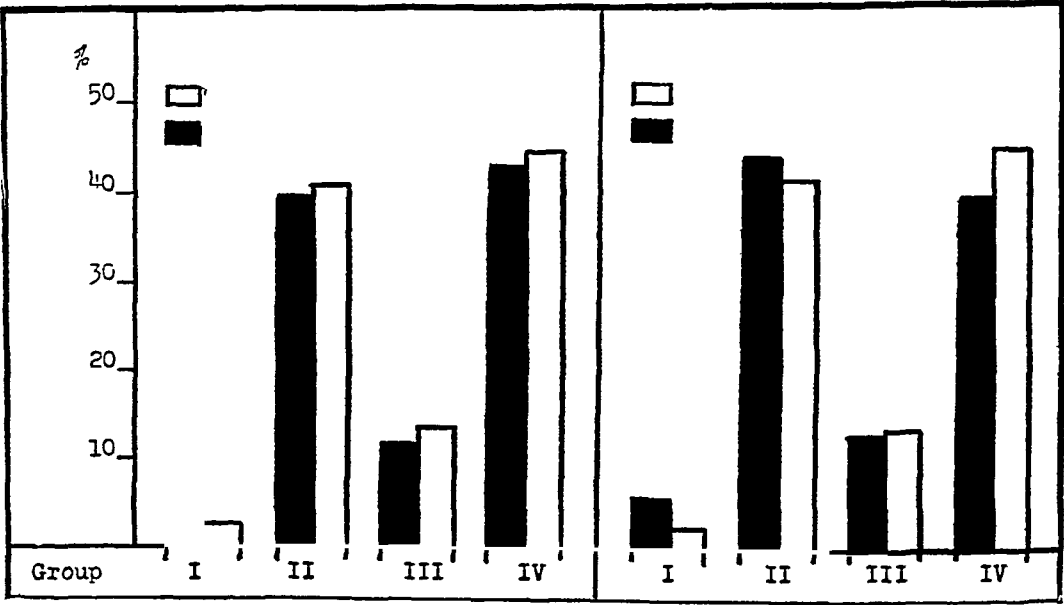
In view of the possible relation of tuberculosis to the so-called asthenic or phthisical bodily habitus, analysis was made also from this

6 Sanford, A. H. Blood Transfusion. Indications for Its Use, Methods of Selecting Donors and a Brief Consideration of Technique, *M. Clin. N. Amer.* 3:801 (Nov.) 1919. Culpepper, W. L., and Ableson, M. Report on Five Thousand Bloods Typed Using Moss's Grouping, *J. Lab. & Clin. Med.* 6:276 (Feb.) 1921.

standpoint In this connection it should be mentioned, however, that diagnoses of habitus, although painstaking, were made impressionistically and without the application of formal anthropometric procedures, also that our total series of asthenics is admittedly rather small

TABLE 2—*Distribution of the Four Blood Groups in Tuberculous Persons Compared with the Distribution in Normal Persons*

Subjects	Number	Blood Groups (According to Moss)			
		I Percentage	II Percentage	III Percentage	IV Percentage
Nontuberculous					
Average	9,600	5.8	38.7	11.3	44.2
European average	8,325	4.6	43.4	12.8	39.2
Tuberculous					
Total	400	2.3	40.2	13.5	44.0
European type	373	2.4	39.6	12.9	45.1
Asthenic (total)	120	3.4	35.8	15.8	45.0
Nonasthenic (total)	280	1.8	42.1	12.5	43.6
Productive (total)	123	2.4	37.4	17.1	43.1



Distribution of the four blood groups in tuberculous persons compared with the distribution in normal persons The black columns on the left side of the chart represent the distribution of the blood groups in the general average of American workers, the white column, the distribution in the total series of tuberculous subjects On the right side of the chart, the black column represents the distribution in the average European subject, the black column, the distribution in tuberculous European subjects

However, subject to the possible limitations of these factors, no essential differences are apparent between the asthenic and the nonasthenic tuberculous groups, although it might be said perhaps that the former seems to be slightly lower in group II

In view of the possible relation between habitus and the so-called exudative and productive types of pulmonary tuberculosis,⁷ an analysis

7 Pinner, Max (Detroit Municipal Sanatorium) Personal Communication

of the blood grouping in these types was originally planned. Unfortunately, the distribution of cases with reference to these two types was not such as to permit satisfactory comparison. It might be mentioned, however, that the series of 123 cases of the productive form does not differ noticeably from the total or asthenic formulas.

In conclusion it would seem that if this series may be regarded as satisfactory, no specific relationship can be established on the basis of the ordinary standards between blood type and tuberculosis. In corollary, from the standpoint of constitution, if there is any specific relationship between tuberculosis and genotypic physiologic pattern, this does not appear to include the quality of blood type.

It might be of some interest possibly to investigate such a series from the standpoint of Guthrie and Huck,⁸ according to whom twenty-seven blood groupings are biologically possible, instead of the four ordinarily assumed.

8 Guthrie, C. G., and Huck, J. G. On the Existence of More than Four Isoagglutinin Groups in Human Blood, *Bull. Johns Hopkins Hosp.* **34**: 37, 80, 128 (Feb., March, April) 1923.

THE OCCURRENCE AND SIGNIFICANCE OF ELECTRO-CARDIOGRAMS OF LOW VOLTAGE *

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The increasing use of the electrocardiograph in the clinical study of heart disease has brought forth many valuable graphic signs in the identification and the corroboration of myocardial disease, and also important facts bearing on prognosis

From time to time various observers have called attention to the relationship of electrocardiograms of low voltage to disease of the myocardium (Carter,¹ Pardee and Master,² Lutembacher,³ White and Burwell,⁴ Clerc and Bascouret,⁵ Oppenheimer and Rothschild⁶) Low voltage electrocardiograms have been recorded in patients with pericardial effusions, returning to normal after paracentesis and subsequent improvement in the patient's condition Oppenheimer and Mann⁷ also called attention to them in connection with extensive pericardial and pleuropericardial effusions The occurrence of low voltage records in myxedema and cretinism has been described by Zondek⁸ and by Thacher and White⁹

A recent report by Sprague and White¹⁰ was based on fifty-seven cases observed during eleven years at the Massachusetts General Hos-

* From the Section on Cardiology, Mayo Clinic

1 Carter, E P Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborization, *Arch Int Med* **22** 331 (Sept) 1918

2 Pardee, H E B, and Master, A M Electrocardiograms and Heart Muscle Disease, *J A M A* **80** 98 (Jan 13) 1923

3 Lutembacher, R The Heart in Hypertension, *Bull med* **31** 616, 1922

4 White, P D, and Burwell, C S The Clinical Significance of Changes in the Form of the Electrocardiogram, *M Clin N Amer* **4** 1839, 1920-1921

5 Clerc, A, and Bascouret, M Les anomalies des complexes ventriculaires electriques et leur importance pronostique dans le cours de l'insuffisance cardiaque, *Rev de med* **41** 587, 1924

6 Oppenheimer, B S, and Rothschild, M A The Value of the Electrocardiogram in the Diagnosis and Prognosis of Myocardial Disease, *Tr A Am Phys* **39** 247, 1924

7 Oppenheimer, B S, and Mann, Hubert An Electrocardiographic Sign in Pericardial Effusion, *Proc Soc Exper Biol & Med* **20** 431, 1923

8 Zondek, Hermann Das Myxodemherz, *Munchen med Wchnschr* **65** 1180, 1918

9 Thacher, C, and White, P D The Electrocardiogram in Myxedema, *Am J M Sc* **171** 61, 1926

10 Sprague, H B, and White, P D The Significance of Electrocardiograms of Low Voltage, *J Clin Investigation* **3** 109, 1926

pital The majority (thirty-four) were of the arteriosclerotic type of heart disease, ten were classified as hypothyroidism and thirteen as miscellaneous The total mortality in this group was 49 per cent In eleven cases the cause of death was definitely attributed to heart disease, and in six others it was presumably due to heart disease, the cause of death in six cases was uncertain These authors did not observe electrocardiograms of low voltage (excluding the temporary effect in hypothyroidism) in patients with normal hearts, and concluded, therefore, that such electrocardiograms are of diagnostic and prognostic importance in forming an opinion of the myocardial capacity of any person In certain of the cases, however, there were associated electrocardiographic abnormalities, such as flutter, incomplete bundle-branch block, auricular fibrillation, complete heart block and significant T-wave negativity These abnormalities are in themselves important and significant, and when independent of records of low voltage are indicative of myocardial disease They are of definite prognostic importance

MATERIAL FROM THE MAYO CLINIC

From a complete survey of all the cases in which electrocardiographic examinations were made at the Mayo Clinic from Aug 1, 1914, to Nov 1, 1926, it was found that 140 of them were cases in which low voltage records were unassociated with other significant graphic abnormalities, an incidence of 0.3 per cent In our selection of cases we followed rigidly the criteria of Sprague and White, accepting those cases only in which the QRS deflections did not deviate more than 5 mm in either direction from the base line in any of the three customary leads The difference in electric potential was therefore not greater than 0.0005 volt All records were standard, that is, a string deviation of 1 cm for each millivolt of current

All records displaying flutter, auricular fibrillation, incomplete bundle-branch block, significant T-wave negativity, complete and partial heart block, delayed auriculoventricular conduction and the ectopic tachycardias were rejected

CARDIAC DISEASES

There were twenty-one cases of arteriosclerotic cardiac disease, sixteen patients were men and five women The youngest was 44, the oldest 80, and the average age in the group was 64 There were two cases in which angina pectoris occurred and eight in which there was congestive heart failure

Information has been obtained regarding fifteen patients Five (33 per cent) have died from heart disease in an average of one and one-half years One death was not related to the heart, and the

cause of another death was not obtained. Eight patients (53 per cent) are alive, seven report their health improved, while that of one is unchanged.

At necropsy in one case marked sclerosis of the coronary arteries was found. The heart was hypertrophied, weighing 679 Gm. This was the only case of hypertension in the group. The myocardium showed fatty changes.

Hypertensive Cardiac Disease—There were nine cases of hypertensive cardiac disease. Six patients were men and three were women. The youngest was 51, the oldest 65 and the average age 58. Only two patients presented the syndrome of congestive failure.

Five patients have been traced. One patient died from heart disease (20 per cent), but the date of death is not known. The remaining four patients (80 per cent) report their condition as being improved.

Rheumatic Endocardial Valvular Disease—There were six cases of chronic endocardial valvular disease. The lesions were stenotic in all, involving the mitral valve in five cases and the aortic valve in one case. Two patients were men, and four were women. The youngest patient was 19, the oldest 49, and the average age was 34. Three patients had congestive heart failure.

Data have been obtained regarding four patients. Two (50 per cent) died from heart disease in an average of three and one-half months from the time of our observation. The other two patients are improved.

Syphilitic Aortitis—There were five cases of syphilitic aortitis. Four patients were men, and one was a woman. Their average age was 38. These patients were all up and about, and their cardiac handicap was relatively slight. None had congestive heart failure or the anginal syndrome.

Three patients have been traced. One died from pneumonia, the other two patients reported that their condition was improved.

Aneurysm of the Thoracic Arch—There was only one case of aneurysm of the aortic arch, that of a man aged 51. The aneurysm was large, but the patient reports his condition as being unchanged.

Adherent Pericarditis—There were two cases of adherent pericarditis, both in women, aged 43 and 54, respectively. One patient had congestive heart failure. The one patient heard from reports her condition improved.

Focal Myocarditis—There was one case of focal myocarditis. The patient, a woman, aged 24, died from this trouble, which occurred during the course of a severe infectious polyarthritis. Necropsy revealed extensive focal myocarditis, terminal bronchopneumonia and diffuse nephritis.

DISEASES OTHER THAN CARDIAC

The remaining ninety-five cases form a miscellaneous group, and in the majority of cases no evidence of cardiac disease existed, while in those with symptoms and signs of cardiac disease the degree of damage was minimal. It is necessary to discuss this group rather fully in order to show the diversified character of the cases and the relationship of low voltage electrocardiograms in apparently normal hearts to those in which cardiac disease probably existed.

Diabetes Mellitus—Electrocardiograms of low voltage occurred in eighteen cases of diabetes mellitus. Fourteen of the patients were men and four were women. The youngest patient was 17, the oldest 72, and the average age was 54. Only three patients presented symptoms of cardiac insufficiency, and none to the degree of congestive failure. The objective cardiac examinations of these patients showed only slight, if any, cardiac enlargement and but slight muffling of the heart tones. The remaining fifteen patients did not have cardiac complaints and did not present symptoms justifying the diagnosis of organic heart disease.

It may be argued, however, owing to the relatively high incidence of arteriosclerosis in diabetic patients that many of the patients had arteriosclerotic cardiac disease. Such an argument is presumptuous in view of the facts at hand.

Fourteen patients were traced. One death only (7 per cent) could be attributed to cardiac disease. Three patients died from diabetes. Ten patients (71 per cent) are alive, five are improved, the health of three is unchanged and two are worse.

Chronic Nephritis—Thirteen patients, seven men and six women, had chronic nephritis, and in only two instances was hypertension associated. The youngest patient was 32, the oldest 67, and the average age was 51. There was evidence of varying degrees of cardiac insufficiency in all but one case, although in no instance was the syndrome of congestive failure noted. In no case was there well defined objective evidence of cardiac disease.

Ten patients have been traced. Only one death (10 per cent) resulted from heart disease, six patients died from nephritis and three patients (30 per cent) are living, one is improved, and two are worse.

One death from nephritis occurred nine months after the electrocardiogram was obtained. Necropsy showed glomerulonephritis, chronic nephrosis, right pleuritis, bilateral hydrothorax and ascites, and terminal pericarditis. The heart was essentially normal.

Chronic Cholecystitis with Lithiasis—Low voltage records were obtained in five cases of chronic cholecystitis with lithiasis. Three of the patients were men, and two were women. The youngest patient

was 37, the oldest 67, and the average age was 43. None of the patients presented cardiac symptoms and examination disclosed no evidence of heart disease.

Four patients have been traced; all are alive and apparently in good health.

Portal Cirrhosis—There were four cases in this group. All the patients were men, the youngest being 26, the oldest 61. The average age was 45. The patients all complained of dyspnea and had ascites, but the symptoms were not the result of primary cardiac disease.

Data have been obtained regarding three patients. One died from cirrhosis, two are alive and report their conditions as unchanged.

Chronic Infectious Arthritis—Chronic infectious arthritis occurred in three cases. Two of the patients were women, and one was a man. The youngest patient was 42, the oldest, 60, the average age was 50. No cardiac symptoms were elicited in any of the cases, nor did objective examination of the hearts reveal evidence of disease. All the patients are alive.

Pericious Anemia—There were three cases in this group, two of the patients were men and three were women. The ages were 52, 58 and 62, respectively. All the patients have died from this disease. In one case in which necropsy was performed, the heart was found to be normal.

Exophthalmic Goiter—Low voltage electrocardiograms resulted in only three cases of exophthalmic goiter. There were two women and one man. All the cases occurred during the fourth decade of life. Two patients had congestive heart failure. Thyroidectomy was performed eventually in all instances. Two patients have been traced. One patient died from tetany two years after operation, and the other is alive and well.

Adenomatous Goiter Without Hyperthyroidism—Three cases occurred in this group, one of the patients was a man and two were women. The ages ranged from 38 to 52. There were no cardiac symptoms or signs of heart disease in any case. All the patients are alive and well.

Myxedema—There were two cases of high grade myxedema. This observation, in the absence of organic heart disease, has been emphasized by White and Thacher and others. The patients were both women, aged 40 and 44, respectively. No evidence of organic heart disease existed. Both patients are alive and well and are under treatment.

Low Basal Metabolic Rate (Not Myxedema)—There was only one case in this group, that of a man, aged 47. There was no evidence of organic heart disease. No information regarding this patient is available.

Syphilis of the Central Nervous System—There were two cases in this group, both patients were men, aged 50 and 57, respectively. No evidence of cardiac disease existed. Both patients are alive, the condition of one is improved, while that of the other is worse.

Addison's Disease—In this group there were three cases, all the patients were men from 31 to 50 years of age. Two patients complained of shortness of breath, which was probably related to the associated asthemia, as no evidence of heart disease was demonstrable. Two patients died from Addison's disease, and the other is alive and somewhat improved on epinephrine therapy. Necropsy in one case revealed no cardiac changes.

Secondary Anemia—Two cases of moderately severe secondary anemia were included in this series. They were both in women in the fourth decade of life. No evidence of cardiac insufficiency existed. One patient that was traced is dead, but the cause of death was not ascertained.

Cancer—Two cases of cancer occurred in this group. Neither patient was cachectic. The stomach was the seat of cancer in one and the hepatic flexure of the colon in the other. Both were men, aged 36 and 68, respectively. There was no evidence of cardiac disease in either case. Both patients are alive, seventeen months and five years after operation.

Mediastinal Lymphosarcoma—There was one case of mediastinal lymphosarcoma in a man, aged 36. There was no evidence of organic heart disease. Death occurred from the malignant process fifteen months after observation.

Pulmonary Emphysema—A case of pulmonary emphysema occurred in a man, aged 58. No observations indicative of heart disease were demonstrable. No word has been received from this patient.

Postoperative Ventral Hernia—Postoperative ventral hernia was seen in one patient, a woman, aged 61. She presented no evidence of heart disease. She is alive and well seventeen months after operation.

Chronic Nervous Exhaustion—This group comprised thirteen cases, one patient was a man and twelve were women. The youngest patient was 27, the oldest 50, and the average age was 40. In no instance did evidence of heart disease exist. Ten patients regarding whom information has been received are alive.

Benign Prostatic Hypertrophy—A man, aged 66, had benign prostatic hypertrophy. He presented no symptoms or objective evidence of heart disease. He was relieved by operation, and is alive and well eighteen months after the examination.

Miscellaneous Group—In this group there were fourteen cases. These included patients in whom examination did not disclose any

pathologic condition and patients with constipation and vague abdominal complaints. There were nine men and five women, their ages ranged from 11 to 67 years. No evidence of heart disease existed in any case. The nine patients who have been traced are all living.

COMMENT

It is of interest to note that electrocardiograms of low voltage independent of significant graphic abnormalities were less frequently associated with frank cardiac disease than with other diseases. The incidence was approximately 1/2. Another striking observation is the fact that among the patients with primary cardiac disease nine, or 30 per cent of those traced, are known to have died from cardiac disease. This is a smaller percentage than one would anticipate in a group of this type. Among the patients with various types of diseases, only seventeen (2 per cent) showed evidence of heart disease, and of the seventy traced, only two (3 per cent) died from heart disease.

These data, we believe, indicate that electrocardiograms of low voltage unassociated with other electrocardiographic abnormalities do not deserve the emphasis accorded them by some authors, and that they occur in records of normal hearts. Their occurrence in organic heart disease apparently does not indicate unusually serious disease, and the mortality figures in this study fail to justify much prognostic importance to their occurrence. It is possible, however, that the transition of complexes of normal voltage to those of low voltage during the course of heart disease may be significant. More records showing this phenomenon are necessary before definite conclusions are justified.

SUMMARY AND CONCLUSIONS

This study comprises 140 cases presenting electrocardiograms of low voltage. This in our experience is an incidence of 0.3 per cent. All cases presenting associated abnormalities, such as auricular flutter, auricular fibrillation, incomplete bundle-branch block, significant T-wave negativity, complete heart block, partial heart block, delayed auriculo-ventricular conduction and the ectopic tachycardias, were excluded in this study. These associated observations in themselves are significant, and when considered in conjunction with records of low voltage they are confusing, and obscure the true issue. The criterion for the selection of cases was a record in which the QRS deflection did not deviate more than 5 mm in either direction from the base line in any of the three customary leads. All records were standard, that is, a string deflection of 1 cm corresponding to 1 millivolt of current.

There were forty-five cases (32 per cent) in which cardiac disease predominated, including (1) arteriosclerotic cardiac disease, 21 cases (2) hypertensive cardiac disease, 9 cases, (3) rheumatic endocardial

valvular disease, 6 cases, (4) syphilitic aortitis, 5 cases, (5) aneurysm of the thoracic arch, 1 case, (6) adherent pericarditis, 2 cases, and (7) focal myocarditis, 1 case

The large group was composed of ninety-five cases (68 per cent) of various types of disease (1) diabetes mellitus, 18 cases (2) chronic nephritis 13 cases (3) chronic cholecystitis with lithiasis, 5 cases (4) portal cirrhosis, 4 cases, (5) chronic infectious arthritis, 3 cases, (6) pernicious anemia, 3 cases, (7) exophthalmic goiter, 3 cases, (8) adenomatous goiter without hyperthyroidism, 3 cases, (9) myxedema, 2 cases, (10) low basal metabolic rate (not myxedema), 1 case, (11) syphilis of the central nervous system, 2 cases (12) Addison's disease, 3 cases, (13) secondary anemia, 2 cases, (14) cancer, 2 cases (15) mediastinal lymphosarcoma 1 case, (16) pulmonary emphysema, 1 case, (17) postoperative ventral hernia, 1 case, (18) chronic nervous exhaustion 13 cases, (19) benign prostatic hypertrophy, 1 case, and (20) miscellaneous group of vague abdominal complaints and negative examinations, 14 cases. In this group only 17 cases (3 per cent) revealed evidence of organic heart disease

The cardiac mortality among the group with cardiac disease was 30 per cent, whereas the cardiac mortality in the group comprised of various diseases was 2 per cent

From the data submitted here it is not justifiable to conclude that electrocardiograms of low voltage unassociated with other graphic abnormalities indicate serious myocardial disease or are of serious prognostic importance

PRIMARY CARCINOMA OF THE LUNGS

FURTHER STUDY, WITH PARTICULAR ATTENTION TO INCIDENCE,
DIAGNOSIS AND METASTASES TO THE CENTRAL
NERVOUS SYSTEM

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Primary carcinoma of the lungs has become a clinical and pathologic entity of importance only in the last two decades. The pathologist of the nineteenth century was apparently under the influence of Virchow's statement to the effect that those organs which are frequently the seat of a metastatic involvement by malignant tumors are only in rare instances the seat of a primary new growth. The lungs were usually quoted as an example. Since from the circulatory point of view these organs are the convergent point of the body, malignant cells which happened to invade the blood or lymph streams invariably reach the lungs, where they form secondary nodules or masses, the latter not infrequently overshadowing that of the primary growth. Moreover, the failure of the pathologist to demonstrate grossly a secondary involvement of the lung by tumor is at present not regarded as being conclusive proof of the actual absence of tumor in the lungs. Numerous investigators¹ have shown that with tumor elsewhere clumps of blastomatous cells (metastatic) can almost always be detected in the lungs on careful histologic investigation.

The foregoing should lead, then, to the belief that whenever, in the presence of a widespread tumor anywhere in the body, a tumor is found in the lungs, the lesion in the latter ought to be considered as metastatic.

With improved pathologic and clinical methods of investigation, however, this belief has been refuted, and recently evidence has accumulated to show that primary carcinoma of the lungs is of relatively frequent occurrence. Nevertheless, the suddenness with which it has emerged from obscurity has impressed observers. It is claimed that the tumor in these organs possesses peculiarities uncommon to epithelial malignant disease found elsewhere in the body. The most debated points at present are its incidence, the methods by which it can be diagnosed in the clinic and, finally, the occurrence of metastases. These three points will be considered separately.

¹ From the Surgical and Pathological Departments of the Peter Bent Brigham Hospital and the Medical Clinic of the Massachusetts General Hospital.

¹ Schmidt, M. B. Verbreitungswege der Carcinoma, Jena, 1903. Goldmann, E. E. Studien zur Biologie der Bosartigen Neubildungen, Beitr. z. klin. Chir. 72 1, 1911.

I INCIDENCE

Recent literature abounds with reports on primary carcinoma of the lungs. A startling increase in primary pulmonary cancer has been noted at necropsies, and this is said to be out of proportion to cancer in general. The published statistics include material from the largest clinics, particularly those of Germany, extending over a long period of time.

In 1920, Lubarsch² collected reports of 450 cases from the German literature, and found the condition in 4.5 per cent of all necropsies. Similarly, Seyfarth,³ in 1924, reported 307 cases from the Pathologic Institute of Leipzig alone, this figure representing 8 per cent of all necropsies performed in that institute.

Of particular interest are the 246 cases reported by Kikuth,⁴ whose necropsy material extended over a period of thirty-five years (from 1889 to 1923). According to Kikuth, primary carcinoma of the lungs represents 9.5 per cent of all cases of cancer in the Pathologic Institute.

TABLE 1—*The Incidence of Primary Carcinoma of the Lungs in Hamburg-Eppendorf-Krankhaus*

From 1889 to 1899,	10	primary cancers of the lungs
From 1900 to 1911,	90	primary cancers of the lungs
From 1912 to 1923,	146*	primary cancers of the lungs

* The yearly number of necropsies in Hamburg doubled from 1889 to 1923.

of the Hamburg-Eppendorf Hospital. In 1923, the number of primary pulmonary cancers equalled one third of the number of carcinomas of the stomach found at necropsies in this large municipal hospital. Figure 1, taken from Kikuth, illustrates the rapid increase in the number of these primary growths in Hamburg-Eppendorf.

There is another municipal hospital in Hamburg, the Hamburg-Barmbeck, which is about as large as the Hamburg-Eppendorf, and which deals with a similar type of patient. In a recent investigation, Breckwoldt^{4a} reached the conclusion that the incidence of primary pulmonary cancer in this hospital has not changed since the opening of the institution in 1913. The same author, by carefully analyzing the figures and charts as given by Kikuth, states that the increase of this disease noted in the Hamburg-Eppendorf is only apparent.

² Lubarsch, O. *Einiger zur Sterblichkeits-und Leichenöffnungs-statistik*, Med. klin. **10** 299 (March 9) 1924.

³ Seyfarth. *Lungenkarzinome in Leipzig*, Deutsche med. Wchnschr. **50** 1497 (Oct. 31) 1924.

⁴ Kikuth, W. *Ueber Lungencarzinome*, Virchows Arch. f. path. Anat. **255**: 107, 1925.

^{4a} Breckwoldt, Richard. *Zur Frage der Zunahme der Lungenkrebse*, Ztschr. f. Krebsforsch. **23** 122, 1926.

Though dealing with smaller figures, reports from other clinics in Europe and in this country are, however, not less expressive as to the frequency of primary pulmonary cancer. These statistics, showing an incidence of from 5 to 6 per cent of all necropsies, are particularly impressive when compared with earlier figures given by Fuchs⁵ and Passler⁶. In 12,307 necropsies performed in Breslau from 1854 to 1885, Fuchs found primary carcinoma of the lungs in only 0.055 per cent, Passler found 0.18 per cent among 9,246 necropsies performed in Munich from 1881 to 1894.

The relative frequency of this disease as seen at present in the clinic and at necropsy, as compared with old observations, is beyond any contest. The question arises, however, whether the noted increase

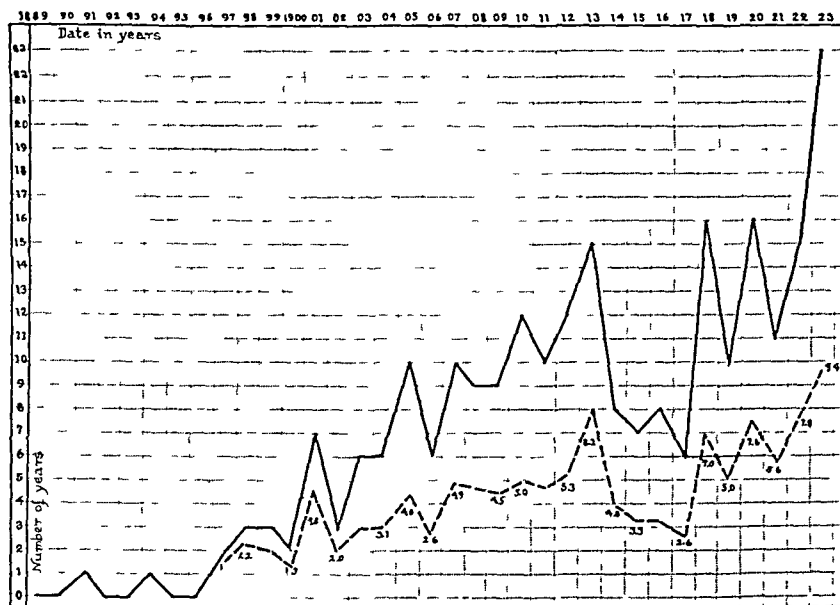


Fig 1—Rapid increase in the number of primary growths in Hamburg-Eppendorf (Kikuth). The solid line indicates incidence of primary carcinoma of the lungs, the broken line, the percentage relationship of primary carcinoma of the lungs to all carcinoma.

is an actual, that is, absolute increase in the occurrence of carcinoma in general and of primary carcinoma of the lungs in particular, or whether the increase is only apparent.

The rise in the morbidity and mortality from cancer in general for the last two or three decades has been heralded by various investigators. Some observations (in this country) are to the effect that cancer is steadily increasing in frequency, the increase being a real

5 Fuchs. Beitr. z. Kenntnis des Primären Geschwulstbildungen in der Lunge, Inaug. Dissert., Munich, 1886.

6 Passler, H. Ueber das Primäre Carcinome der Lunge, Virchows Arch. f. path. Anat. 146: 191, 1896.

one In a recent study, Wells⁷ attributes no value to the existing cancer statistics in this country European observers like Lubarsch (Germany), Staehelin (Switzerland) and Ménétrier (France) are either skeptical or actually opposed to the idea that the increase in the incidence in cancer noted lately is a real one Lubarsch,² in his investigation on the occurrence of cancer in Germany, could draw no definite conclusions as to its increase Hanf,^{7a} in a work inspired by Lubarsch, recently investigated the incidence of primary cancer of the lungs in the Pathologic Institute of the University of Berlin Her figures show that there was no increase in this malignant disease in this institute for the last twenty years Staehelin,⁸ referring to noted Swiss statisticians, is of the opinion that cancer is not increasing in frequency He quotes Jessen, who investigated the cancer mortality in Basel during the period from 1870 to 1919, with a negative result as to the rise in the morbidity and mortality from cancer Since the appearance of Staehelin's paper, investigations for other cities in Switzerland were reported by Renaut⁹ and Carriere,¹⁰ who confirmed the observations made by their predecessors

TABLE 2—*Incidence of Cancer in Lausanne (Renaut)*

	1901	1920		1901	1920
Cancer of the tongue	50	55	Cancer of the pancreas	48	78
Cancer of the uterus	355	321	Cancer of the lungs	15	50
Cancer of the vagina and vulva	21	18	Cancer of the ovaries	58	78
Cancer of the intestines	190	338			

In France, Ménétrier¹¹ affirms that cancer is as frequent now as it was a century ago This scientist bases his opinion on a careful investigation of Parisian statistics and also on his fifty years of clinical and pathologic observations

It is remarkable that the figures in the majority of European statistics show an increased incidence in visceral cancer and no corresponding rise in external cancer Table 2, taken from Renaut,⁹ shows the

7 Wells, G H Relation of Clinical to Necropsy Diagnosis in Cancer and Value of Existing Cancer Statistics, J A M A **80** 737 (March 17) 1923, Cancer Statistics as they Appear to Pathologist, *ibid* **88** 399 (Feb 5) and 476 (Feb 12) 1927

7^a Hanf, Dora Zur Frage der Zunahme der Lungenkrebse in den letzten Jahren, Virchows Arch f path Anat **264** 366, 1927

8 Staehelin, R Ueber die Zunahme des Primären Lungenkrebses, Klin Wchnschr **4** 1853 (Sept 24) 1925

9 Renaut, A Einige Belege und Betrachtungen zur Verbreitung und Statistik der Krebses, etc, Schweiz med Wchnschr **56** 106 (Feb 6) and 132 (Feb 13) 1926

10 Carriere, quoted by Imbert L'augmentation du frequence du cancer est-elle reelle ou apparent? Bull de l'assoc franç pour l'etude du cancer **15** 141 (April) 1926

11 Menétrier, M P La frequence du cancer, Bull Acad de med **95** 177 (Feb 23) 1926

incidence in Lausanne of these two types of cancer in the years 1901 and 1920, respectively

In England and Wales, the rate of cancer of the skin for men over 35 in 1868 was 45.7, and in 1909 it was 43.5. The rate for women over 35 years of age for cancer of the breast, uterus and ovaries was 117 in 1888, in 1909, it was 121, and in 1919, it was 127.

The foregoing may be explained plausibly on the basis that, with the improvement of modern methods of diagnosis, deep seated visceral cancer is more readily discovered now than formerly. Thus, for instance, the increase in the occurrence of prostatic carcinoma for the last twenty years is due to progress in genito-urinary surgery resulting in an increased number of removed prostates examined histologically. On the other hand, a noticeable decrease of carcinoma of the thyroid is due to early extirpation of hyperplastic glands, which in a number of instances would have become malignant.

Opinions are also to the effect that the increase in the occurrence of cancer analogous to the increase in degenerative disease in general is due to increased human longevity.

Thomas,¹² for instance, relates that for centuries before and after the time of King Tut-Ankh-Amen down to the discovery of America, the average length of life was eighteen years, at the time of the French Revolution, it had increased to thirty-three years, at the time of the Civil War, it had advanced to approximately forty-five years, at present, it is about fifty-seven years. Ten of these added years, says Thomas, have been contributed during the last two decades. The importance of such facts is evident in connection with the well known "cancer age."

In a comprehensive review on the progress of medicine, the French clinician and hygienist Apert¹³ also stresses the fact that the increased incidence of cancer during the last two or three decades is due partly to the lengthening of human life.

From the foregoing, it would appear that cancer in general, and primary pulmonary cancer in particular, owes its increase (1) to improved medical training and better diagnostic methods, (2) to improvement in sociologic conditions of the masses leading to their larger attendance at hospitals, and (3) to progress in hygiene and preventive medicine resulting in increased human longevity.

The increase, therefore, of all cancer, as well as that of primary carcinoma of the lungs, is in all probability more apparent than real.

12 Thomas, B. A. The Influence of Urology on Longevity, *J. A. M. A.* 86: 1957 (June 26) 1926.

13 Apert, E. La mort recule, *Rev. de deux mondes*, 27: 121 (May) 1925.

II DIAGNOSIS

The clinician of the nineteenth century was poorly aided with accessory methods for the diagnosis of pulmonary diseases. The tubercle bacillus, which is in reality the single criterion in making the diagnosis of pulmonary tuberculosis certain, was discovered in 1882. The roentgen ray as an effective aid in the diagnosis of diseases of the chest has been applied successfully in the clinic only for the last fifteen years. Bronchoscopy is of still more recent origin, and the use of iodized oil 40 per cent is as yet in its rudimentary state. Surgical exploration in obscure or doubtful cases, as practiced in the diagnosis of abdominal or pelvic organs, has not been applied to intrathoracic pathologic conditions, since the lungs have been considered from the surgical standpoint as a *noli me tangere*. For this reason, the pathology of the lungs has remained practically an unexplored field.

The diagnosis of primary carcinoma of the lungs today is based on (1) clinical data, which include the history, symptomatology, course and physical signs, and (2) laboratory methods, such as bacteriologic examination of expectorated material, roentgen-ray examination, bronchoscopy and intratracheal injection of iodized oil 40 per cent.

There has been little advance for the last twenty-five years in regard to clinical means in the diagnosis of pulmonary diseases, and the interpretation of physical signs found in these organs in pathologic conditions has remained practically unchanged since the time of Laennec. Moreover, in primary carcinoma of the lungs the signs are amazingly scant as compared with the "amount" of tissue involved and the grave character of the lesion. Again, oftentimes they are ambiguous. The cases that follow illustrate the foregoing statements.

CASE 1—In a man, aged 38, the expansion of the lungs was diminished on the left side. Vocal fremitus was diminished on the left side anteriorly and was absent posteriorly. On percussion of the left side, the note was flat from the apex to the angle of the scapula, and dull down to the lower border of the lung as far as the posterior axillary line. Anteriorly, it was dull at the apex up to the second interspace, below that, it was normal for an interspace and then was markedly tympanitic down to the base and along the axillae, as if there were air beneath the pleural cavity. On auscultation, the left side showed diminished bronchial breathing posteriorly at the apex down to the angle of the scapula. Below that, for two or three interspaces, the breath sounds were purely bronchial and close to the ear, at the base, there was distant bronchial breathing. The whispered voice corresponded. Anteriorly, the breath sounds were bronchial down to the third interspace, and below that to the base there was distant bronchial breathing.

At necropsy, a primary cancer occupying the entire apical part of the left lung was found. The rest of the lung, with the exception of the lower segments of the lower lobe, appeared as if it were split vertically in two equal parts. The anterior area was emphysematous and free of tumor, the posterior area was represented by a solid tumorous block.

CASE 2—A man, aged 64, showed on physical examination dulness over the right lower lobe with increased breath sounds, normal whispered voice and decreased tactile fremitus in this area.

At necropsy, Dr Wolbach found a nearly complete occlusion by tumor of the right bronchus 2 cm below the bifurcation. Anteriorly, the wall of the right bronchus was entirely replaced by new growth. The single upper lobe branch of this bronchus which could be traced was also almost entirely occluded by tumor. Below, the bronchus ended abruptly in a diffuse mass of tumor. The new growth, which had replaced the wall of the primary bronchus, extended by direct continuity over the anterior surface of the aorta, forming a layer 1 cm thick which extended upward over the ascending position of the arch. Posteriorly, the lung was atelectatic, containing a few bronchiectatic cavities. The upper lobe was tough and fibrous, with a few nodules at the periphery.

CASE 3—A man, aged 52, showed, on physical examination of the lungs, that the left apex was moderately dull, with a few fine râles, in the right, there was

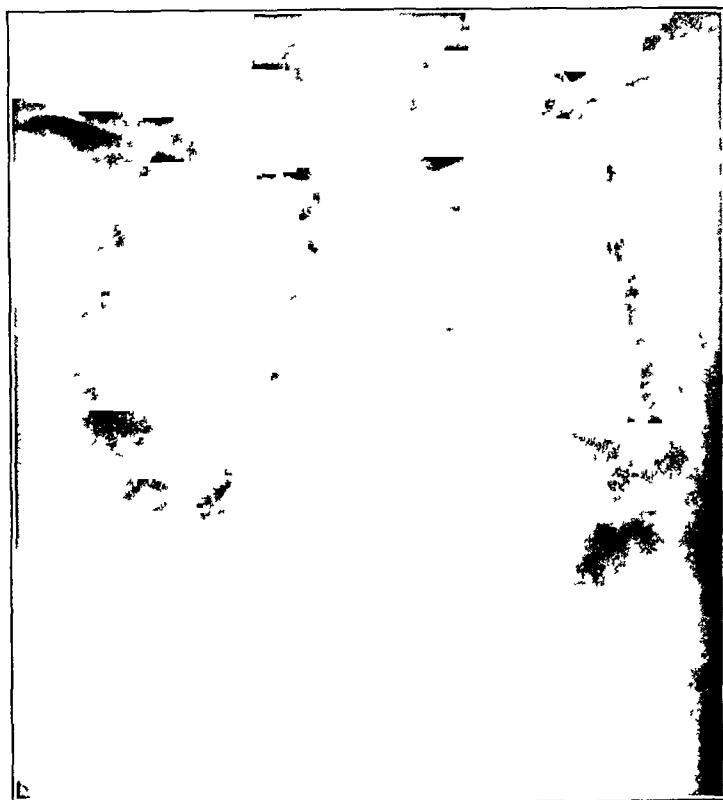


Fig 2 (case 7) —Primary carcinoma of the lungs, showing tumor occupying the base of the left lung. The roentgenogram was taken about two months before death.

dulness and bronchial breathing from the apex to the interior angle of the scapula, with increased voice sounds. Below to the base there was flatness and a complete absence of breath sounds.

At necropsy, the right lung was found to be sclerosed and contracted, occupying only the upper half of the pleural cavity. It was diffusely infiltrated with tumor. The inferior half of the pleural cavity contained a bloody fluid. The left lung was studded with disseminated tumorous nodules, which gave to the lung on palpation a finely granular feel as if it were filled with glass beads.

As seen, the amount and character of the changes found in the pulmonary parenchyma at necropsy in the cases already mentioned are out of proportion to the signs found on physical examination. The same is true of all the cases reported in this paper which came to necropsy.

From the point of view of the symptomatology, primary carcinoma of the lungs may manifest itself in several ways. It may give symptoms referable to the organs of the chest, it is said to run a "silent" course, giving only signs characteristic of a malignant condition anywhere in the body, or again there may be only symptoms due to metastases from the primary growth.

Some reports in this country are to the effect that a correct diagnosis of primary pulmonary cancer can be made readily, provided one keeps in mind the possibility of its occurrence. Grove and Cramer¹⁴ affirm that in a series of twenty-four cases a correct diagnosis was made by the interns of the Cook County Hospital in eight instances, or 33.3 per cent. It is of interest that in 1923 Wells⁷ found in the Cook County Hospital eleven cases of primary pulmonary cancer with only one correct diagnosis. Of the thirteen patients who came to that hospital during the last two or three years (eight of whom came to necropsy), a correct diagnosis by the house officers was then made in seven instances, or in 57 per cent of the cases.

Authoritative European clinicians (de la Camp¹⁵ and Staehelin,⁸ whose opinion I share), admit great difficulties in making a correct diagnosis of primary carcinoma of the lungs. Likewise, the French clinician Rist¹⁶ says that the diagnosis of primary cancer of the lungs is difficult. All the cases of this condition that he has observed have been diagnosed at one time as tuberculosis. In a recent article, Graham¹⁷ affirms that "often the first symptoms of pulmonary carcinoma are those due to abscess." Indeed, there is not a single symptom or a group of symptoms which is not common to tuberculosis as well as to cancer. Loss of appetite, weight and strength, cough, expectoration, fever, etc., are common to phthisis as well as to a number of chronic respiratory infections. A diagnosis, consequently, is made only after a more or less prolonged observation of the patient with all the clinical and laboratory data at hand. In cases 4, 5 and 6, the reports of which follow, the patients' chief complaints were referred to the thoracic organs. From the standpoint of signs and symptoms they were regarded as being more or less typical of a malignant disease of the lungs.

CASE 4—*History of several months of cough, weakness and pain in the right side of the chest. Bronchoscopy. Diagnosis. Primary bronchogenic carcinoma of the right lung.*

14 Grove, J. S., and Cramer, S. E. Primary Carcinoma of the Lungs, *Am J M Sc* **151** 250 1926

15 Camp, de la, O. Zur Klinik der Primären Bronchial Karzinom, *Med Klin* **20** 1270, 1924

16 Rist, E. La différentiation clinique de la tuberculose pulmonaire d'avec les autres affections de voie respiratoires, *Rev de la tuberc* **4** 125, 1926

17 Graham, E. A. The Surgical Treatment of Pulmonary Suppuration in Children, *J A M A* **87** 806 (Sept 11) 1926

History—A Scotch tanner, aged 62, married, was admitted to the hospital complaining of pain in the right lower quadrant of the chest and in the neck. The family history was unimportant. The past history, except for chronic alcoholism, was also negative. The present illness began several months before admission, with weakness and a cough productive of white mucoid sputum. About five months previously, he developed a steadily increasing pain in the right lower quadrant of the chest. At the same time, he became dyspneic. Four months previously, he was so weak as to be obliged to quit his work. Although his appetite had remained good, he lost 20 pounds (9 Kg) in weight during the preceding four or five months.

Physical examination showed a poorly developed and poorly nourished man breathing with short respirations and coughing frequently with considerable distress. The right lung showed slight relative dullness posteriorly over the upper and mid-portions with dullness at the base, so that the lower border of pulmonary resonance on the right was 3 inches (8 cm) higher than on the left. At the base, breath sounds were decreased at the upper edge of the dull area and absent below. Over the slightly dull area above, the breath sounds were slightly louder than on the left. In the right axillary region and in front there was also dullness, with decreased breath sounds. The upper level of this dullness was higher in the back than in the axilla and higher in the axilla than in front. There were no signs of displacement of the mediastinum to either side and no râles. The sputum was mucoid, blood streaked and showed no tubercle bacilli.

Roentgen-Ray Examination—Stereoscopic roentgenograms of the chest showed an ill-defined, dense mass running posteriorly from the right hilum. The symptoms were interpreted as compatible with a primary carcinoma of the root of the right lung or possibly a localized nontuberculous inflammatory process.

Bronchoscopy—The bronchial wall on the right just below the bifurcation was greatly thickened and was somewhat irregular, gradually narrowing down until no bronchial lumen could be seen at the point where the bronchoscope met impossible resistance. A specimen was not removed, but the appearance of the bronchial lumen suggested some malignant process infiltrating the bronchial wall in the region of the main stem of the right bronchus.

This was a typical case of primary carcinoma of the lungs (1) the physical signs found in the chest were few and were not characteristic, (2) the cough was productive of mucoid sputum streaked with blood and was out of proportion to the signs, (3) there was pain in the chest, (4) there was considerable loss of weight in a relatively short period of time, (5) general weakness was present, (6) the roentgen rays pointed out that there was a tumor originating around the hilum of the lung, and (7) the bronchoscope showed a greatly thickened irregular bronchial wall just below the bifurcation, gradually narrowing down until no bronchial lumen could be seen.

CASE 5—Short history of cough and dyspnea. Intratracheal injection of iodized oil 40 per cent. Bronchoscopy with removal of tissue. Diagnosis: Primary carcinoma of right bronchus.

History—A Jewish cobbler, aged 51, married, entered the clinic complaining of belching of "gas" and cough. The past and family histories were unimportant. The present illness began a few weeks before admission with a cough coincident with a cold, which rapidly became persistent, severe and distressing. At the same time, the patient became dyspneic.

Examination showed a man whose respirations were labored, with a definite asthmatic stridor on expiration. He was cyanotic and orthopneic. The right pupil was smaller than the left. Examination of the chest showed flattening of

the right side of the thorax. There was dulness at the base of the right lung extending into the axilla. The breath sounds over this area were distant, and tactile fremitus diminished. The heart and trachea were displaced to the right.

The sputum was abundant, blood-streaked, and negative for tubercle bacilli. The white blood cells totalled 21,000 per cubic millimeter.

A roentgenologic investigation of the gastro-intestinal tract was negative.

Fluoroscopically, the right side of the diaphragm showed paradoxical movement. The observations indicated a partial block of the right bronchus. A reexamination of the chest, after injection of 25 cc of iodized oil 40 per cent, showed a complete block of the bronchus of the right lower lobe and partial block of the bronchi of the middle and upper lobes. The lung on this side appeared emphysematous and distended. Most of the iodized oil had gone into the left base, where the bronchi appeared normal. The impression was that there was a block of the bronchus of the right lower lobe and a partial block of the main bronchus on the right.

Bronchoscopy—A bit of tissue was removed and under the microscope showed a squamous epithelial cell tumor.

The patient remained in the hospital five weeks and was discharged with a diagnosis of primary bronchogenic carcinoma of the right side.

The patient in this case was slightly cyanotic and orthopneic, with a definite asthmatic stridor on expiration. His sputum had a "raspberry-jelly" like appearance, which at one time was considered characteristic of primary carcinoma of the lungs.

Of interest also are the following points: (1) The flattening of the affected side. This was due either to atelectasis of the diseased lung following obstruction of a bronchus by the tumor, or to an obliterating pleuritis as a result of the involvement of the pleura by the new growth. In primary cancer of the lung, both processes may intervene. The significance of this condition as a diagnostic criterion is, however, restricted, since it is liable to occur in numerous pleuropulmonary conditions. (2) The displacement of the heart and trachea. This also is not a feature characteristic of a pulmonary malignant condition only. Chronic cirrhotic pulmonary tuberculosis frequently furnishes the same picture. (3) Inequality of pupils due to paralysis of the sympathetic nerve involved by the new growth. Here again this sign has no value, since it is encountered in a number of organic diseases. (4) The intratracheal injection of iodized oil 40 per cent showed a complete block of the bronchus of the right lower lobe. This is, as far as I am aware, the first case on record in which iodized oil was used in the diagnosis of the primary pulmonary tumor. (5) *Bronchoscopy*. The removal of a bit of tissue is the most reliable criterion, and should be applied whenever possible. Unfortunately, in the majority of cases the tumor starts deep in the pulmonary parenchyma in a small bronchiole, thus making the bronchoscopic examination impracticable.

CASE 6—A history of cough of four months' duration associated with precordial pain. Clinical diagnosis: Primary carcinoma of the left lung. Atelectasis of the left lower lobe. *Bronchoscopy*. Pathologic diagnosis: Squamous epithelial carcinoma of the bronchus.

History—A Jewish tailor, aged 74, entered the hospital for the first time, Dec 22, 1924, complaining of persistent cough. His family history and past history were negative, except for the fact that his father had asthma. His present illness began in September, 1924, when he developed a persistent cough productive of nonmucoid phlegm. The cough increased in intensity, and at the time of admission was almost continuous. At times it was associated with precordial pain, never radiating down the arm and with no substernal distress or discomfort. It was worse when the patient was lying down.

Physical Examination—Dulness in the lungs was present, beginning a little below the angle of the scapula and extending to the base between the scapular line and the midback. Over the axillary region there was no definite dulness except posteriorly, where there was slight dulness at the base. Over the dull area, breath sounds, voice sounds and tactile fremitus were all decreased as compared with the right side. There was no abnormality in the quality of breath or voice sounds over the dull area. The abdomen was normal. No palpable lymph nodes were found in the neck, axillae or groins.

Roentgen-Ray Report—A roentgenogram of the chest showed a high, fixed left side of the diaphragm. The left lung showed an irregular mass at the hilum fading out toward the periphery. The apex and right lung were clear. The impression of the roentgenologist was that there was a primary bronchogenic tumor causing atelectasis of the left lower lobe.

Bronchoscopy—The lumen of the bronchus of the left lower lobe was greatly narrowed by thickening and hyperplasia of the bronchial wall, which at one point appeared to consist of a definite growth from the mucous membrane. A portion of this structure removed showed a new growth made up of squamous epithelial cells.

Clinical Course—The patient suffered exclusively from pain in the chest, which was relieved by morphine. His appetite was good, and the weight remained good. He died eight months after the onset of the first symptoms.

The clinical diagnosis was primary carcinoma of the lung originating in the large left bronchus.

The diagnosis of a primary bronchogenic cancer in this case, as in previous cases, was based on physical examination and observation, as well as on roentgenologic and bronchoscopic examinations.

It was noted in the foregoing that in some instances primary pulmonary cancer may run a silent course, i. e., one in which the patients' complaints are characteristic of a malignant condition anywhere in the body. The patient in case 10 in the series reported previously¹⁸ entered the clinic with the sole complaint of progressive weakness and loss of weight of nine months' duration. These complaints dominated the clinical history during all the patient's stay at the hospital. Similar "silent" cases have been noted by Stachelin,⁸ Letulle¹⁹ and others.

Though the lack of thoracic symptoms in the course of primary pulmonary cancer has been cited by many observers, it must be pointed out that a careful study will almost always elicit signs more or less typical of bronchial irritation or of other intrathoracic disturbance. These signs are unnoticed because of the more dramatic events in the clinical history and the patients' complaints which have overshadowed those

¹⁸ Fried, B. M. Primary Carcinoma of the Lungs, Arch Int Med **35** 1 (Jan) 1925.

¹⁹ Letulle, M. Le poumon, Paris, A. Maloine et Fils, editeurs, 1924.

of the thoracic organs The case that follows is illustrative in this respect

CASE 7²⁰—*Five months' history of pain in the lumbar region and inability to walk Necropsy Primary carcinoma of left lung, with metastases to bones, brain, pleura, liver and suprarenals*

History—A Jewish woman, aged 57, entered the hospital, March 14, 1923, with the complaint of pain in the lumbar region extending down the left leg to the knee, and of inability to walk The family and past history were unimportant A tumor had been removed from the breast twenty-five years previously

The present illness started with a dull, persistent bilateral lumbar pain five months before admission Two weeks later, the pain extended down the left

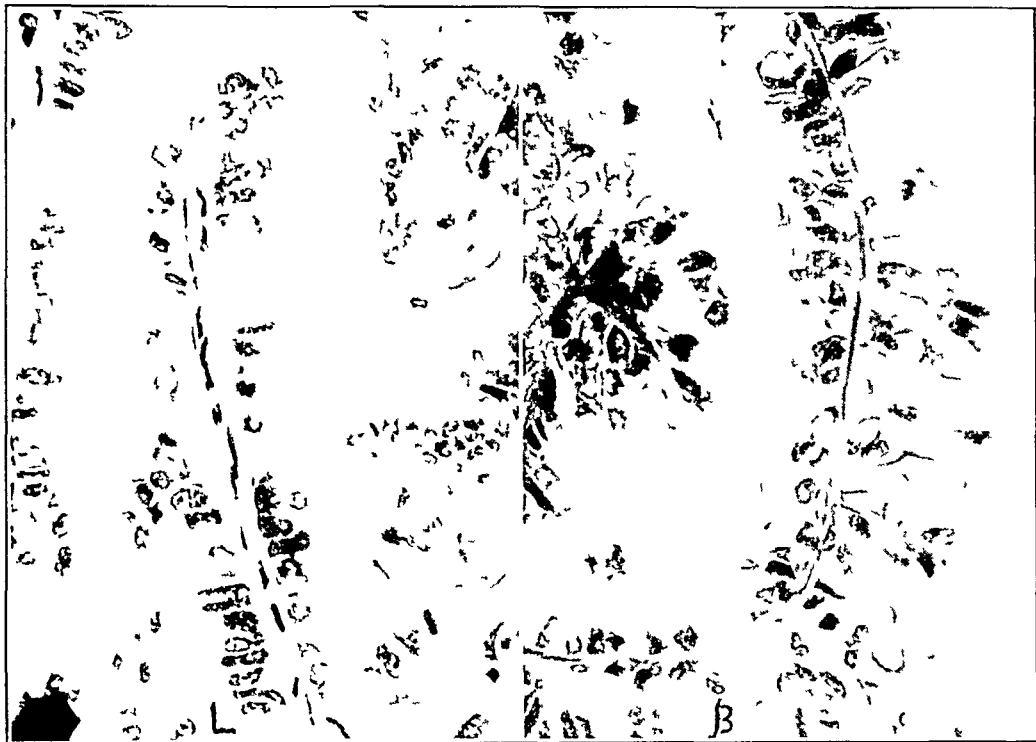


Fig 3 (case 7)—Primary carcinoma of the lungs, showing (L) the histologic structure of the primary tumor in the lungs and (B) the metastases in the brain The similarity should be noted

anterior thigh There had been trouble in walking and night sweats for from eight to twelve weeks, slight hemoptysis had occurred for two weeks

On physical examination, the lungs were normal, the abdomen was spastic, and the left lower quadrant was definitely tender Several small nodules were found on the left side of the cervix uteri The blood pressure was systolic, 110, diastolic, 60 Clinically, no pathologic changes were found Roentgen-ray examination showed an area of consolidation in the left base (fig 3)

Following an operation for myoma of the uterus, the wound healed poorly, owing to infection The patient coughed up blood-tinged sputum The temperature was of a septic character The patient died after seventy-five days in the hospital

The necropsy revealed a primary carcinoma of the left lung occupying the left lower lobe and extending along the posterior axillary line just below the inter-

20 This case and case 8 were reported previously in detail Cf footnote 18

lobar fissure There were metastases to the pleura, bones, liver and suprarenals In the brain a tumor nodule measuring 1.5 cm. in diameter was found in the left posterior parietal region It was definitely adherent to the dura by clot, and its base seemed to have infiltrated the dura in places

The pathologic diagnosis was primary carcinoma of the lungs, metastatic to the brain, bones, pleura, liver and suprarenals

The notion that the first complaints of the patient may be, and indeed frequently are, referred to the metastatic involvement by the tumor is practically unknown In this case particularly, the idea that the bones were the seat of a secondary new growth from somewhere in the body was not even suspected, owing, apparently, to the fact that it concerned a woman, it is still believed that the bones are usually involved by a metastatic cancer from the prostate only It is now known that primary carcinoma of the lungs, as well as of the liver, metastasize readily to bone Older pathologists and surgeons observed frequent involvement of the bones from mammary cancer It is rarely seen now because the tumors of the breast are removed early The metastasis to the brain was not heralded in this case by any signs or symptoms, or possibly it had been overlooked, due to the small size of the tumor

The signs found on examination of the chest were indefinite, and the presence of an area of consolidation at the base of the lungs indicated a pulmonary infarct (It will be remembered that the patient coughed up blood a few weeks before admission)

Here, then, were unquestionable signs and symptoms referable to the organs of the chest They were overlooked (1) because the patient's "alarming" complaints were directed to other organs, and (2) because of the lack of knowledge concerning the frequent occurrence and behavior of primary carcinoma of the lungs, particularly lack of knowledge of its power to give widespread metastases

III METASTASES

A Metastases in General—Primary carcinoma of the lungs possesses a vigorous metastatic power, and its metastases are, as a rule, widely distributed This has been attributed to the facts that (1) the tumor is malignant and its dissemination effected with rapidity, (2) the lungs are abundantly supplied with blood and lymph vessels, i. e., with a rich net of channels facilitating the transport of tumor cells ²¹

21 In a study of a case of primary bronchogenic cancer, Letulle and Jacquelin (Les "embolies bronchiques" cancéreuses, *Presse med* **32** 825, 1924) produced evidence that the transmission of tumor from one lung to the other was effected by way of the bronchi, similar to the occasional propagation of tuberculosis from one lung to another by way of a bronchial embolus—"embolie bronchique"—as described first by the French pathologist, Sabourin The authors have designated this method of metastases as "metastase aerienn"

It seems, however, that in malignant disease, analogous to infectious processes, the host himself has to be taken into consideration. Many years ago, Lubarsch²² noticed that blastomatous cells which had been carried into the circulation grew there only when favored by some factors which he thought emanated from the tumor cells themselves. In his opinion, malignant cells secrete a toxic substance which passes into the circulation, eliminating the factor present in normal human plasma, inhibitory to tumor cells. The fact that the tributary lymph glands in cancer show structural changes of toxic origin long before they have been involved by new growth is, in the mind of Lubarsch, the result of some kind of secretion from the tumor which prepares the terrain for its implantation. He regards the property to form metastases as a consequence of some kind of auto-intoxication.

To be sure, the property of a new growth to metastasize and the abundance of metastases in one or another variety of tumors depend on a number of factors, some of which will probably not be known until the final solution of the problem of a malignant condition. It would appear, however, that the rôle of the organ itself in which the tumor arises is of minor importance in the wide distribution of secondary growths. The liver, for example, gives rise to two varieties of tumors—hepatoma, or carcinoma of the liver cells, and cholangioma, or carcinoma of the bile duct²³. Whereas metastases from the cholangioma are widespread, those from the hepatoma are surprisingly scant. In the epithelium lining the acini of the prostate, two carcinomas of different structure may arise. In one instance, the metastases are abundant, in the other, they are scant. In the lungs themselves a number of cancers do not metastasize at all, while in other cases of pulmonary cancer the regional lymph nodes only are involved by the new growth.

Observations have been made to the effect that the structure of the tumor is an important factor influencing the abundance of metastases. Soft, cellular tumors metastasize more readily than those which are poor in cells and, consequently, hard in consistency. It has also been noticed that malignant disease occurring in extreme old age shows slight predisposition to metastasize widely. Finally, paradoxical as it may appear, the abundance of carcinomatous metastases is generally in an inverse proportion to the rate of growth of the tumor, the slower the rate of growth of the neoplasm the wider are its metastases. In a study

22 Lubarsch, O. Geschwulste Blutveränderungen bei Carcinom. *Ergebn d Allg Path* 2 566, 1895, Über destruierendes Wachstum und Bosartigkeit der Geschwulste, *Ztschr f Krebsforsch* 5 114, 1907.

23 Fried, B. M. Primary Carcinoma of the Liver, *Am J M Sc* 168 24 (Aug) 1924.

of 452 necropsies with cancer somewhere in the body, Kitain²⁴ found that the cancrroid and scirrhus type of carcinoma furnished the highest figures of widespread metastases

In an experimental investigation of the formation of metastases in sarcoma of the hen, Pentimalli²⁵ arrived at similar conclusions. This author found widespread metastases, detected macroscopically (lungs, liver, kidneys) in slowly growing tumors only. In those which grew rapidly, metastases could be disclosed only by animal inoculation of small hemorrhagic foci (red metastases) found mostly in the liver of inoculated birds. Analogous observations were made previously by Haaland²⁶ in experimental transplantation of sarcoma in mice.

This possibly may be accounted for by the fact that rapidly growing tumors usually kill the animal or cause the death of the patient before widespread metastases have time to develop.

Although there are no definite data concerning the approximate duration of the disease in primary carcinoma of the lungs, yet it would appear that its advance is slow. Not infrequently months of clinical observation controlled by roentgen-ray examination show a hardly perceptible advance of the growth. Very likely, then, the wide spread of metastases in primary pulmonary cancer is due also, all other conditions being equal, to its usually slow growth.

B Metastases to the Central Nervous System—In nineteen cases of primary carcinoma of the lungs which I have investigated, extensive metastases to the brain occurred in nine instances, in addition to wide general metastases, the occurrence of which, as said, is common in primary malignant disease of the lung. German authors have noted also that the brain is frequently involved by primary bronchogenic cancer.

Seyfarth³ found involvement of the brain in thirty-two cases that he studied. He does not say whether the brain was examined in all necropsies in his series. Dosquet,²⁷ in a work inspired by Lubarsch, investigated the material of the pathologic institutes of the cities of Berlin (from 1907 to 1920) and Kiel (from 1914 to 1918). Of 105 primary cancers of the lung, 33, or 37.5 per cent, gave metastases to the brain.

The brain was examined in eleven of the nineteen cases that I have investigated. Nine of the eleven cases showed cerebral metastases.

24 Kitain, H. L. Zur Kenntnis der Häufigkeit und der Localization von Krebsmetastasen, etc., *Virchows Arch f path Anat* **238** 288, 1922.

25 Pentimalli, F. Ueber Metastasenbildung beim Hünersarcom, *Ztschr f Krebsforsch* **22** 64, 1924.

26 Haaland, M. Die Metastasenbildung bei transplantierten Sarkomen der Maus, *Ztschr f Krebsforsch* **5** 122, 1907.

27 Dosquet. Ueber die Metastasenbildung bei Primären Lungen und Bronch Krebses, *Virchows Arch f path Anat* **234** 481, 1921.

This is of interest in that cancer, according to the commonly accepted theory, spreads only by way of the lymphatics, which are lacking in the central nervous system

More recent observations, however, are to the effect that the blood stream is much more frequently invaded by cancerous cells than was commonly thought (Schmidt²⁸ and Goldmann²⁹)

My own investigation of the pathologic material at the Harvard Medical School is in complete agreement with that of the authors quoted. Tumor cells were invariably found in the vessels (lumen or wall) of various calibers, and also in the capillaries of almost every case investigated. Figure 4 demonstrates thrombosis of a larger pulmonary vein by cells of a bronchogenic cancer. Carcinomatous cells, as seen, have invaded the vascular coats and have also ruptured the vessel wall. Again, it is of interest to note that in almost every case studied, the brain contained numerous tumor nodules, invading practically every part of the hemispheres and also the cerebellum, which affords definite evidence for hematogenous transport, with possibly "showers" of emboli carried to various structures of the brain.

C The Cause of the Frequent Occurrence of Cerebral Metastases in Primary Pulmonary Cancer—The strikingly frequent occurrence of metastases of the brain in primary carcinoma of the lungs, an occurrence which is relatively rare in extrapulmonary cancers, in addition to the factors mentioned, is particularly favored by the absence of any barrier between the lungs and the brain. A cell embolus from a pulmonary cancer passes, of course, from the pulmonary vein and heart directly into the cerebral circulation. A similar embolus from elsewhere in the body on its way to the central nervous system passes primarily through the "sieve" of the lungs, the latter serving as a barricade, keeping back the advance of the growth.

Cancer of the breast, as shown by Goldmann,²⁹ reaches the lungs with great frequency. The tumor emboli are, however, caught by the pulmonary capillaries in which they are, so to speak, immured. Moreover, they lead frequently to the formation of local infarcts followed by organization and destruction of the metastatic neoplastic cells. This has been confirmed in a recent investigation by Stein.³⁰

Lubarsch affirms that both the lungs and the brain are acid containing organs, and that cells of a pulmonary cancer reaching the brain find themselves, consequently, in conditions favorable to their further development. Burrows,³¹ too, believes that for metastases to localize in

28 Footnote 1 (first reference)

29 Footnote 1 (second reference)

30 Stern, A. Das Schicksal eingeschwemmter Geschwulstzellen in der Lunge, *Virchows Arch f path Anat* **241** 219, 1923

31 Burrows, M. T. The Mechanism of Cancer Metastasis, *Arch Int Med* **37** 454 (April) 1926

distant organs or tissues these points of localization not only must be sites in which the circulating stimulus can collect, but also must contain an ample collection of other nutrient substances for the growth of the cells

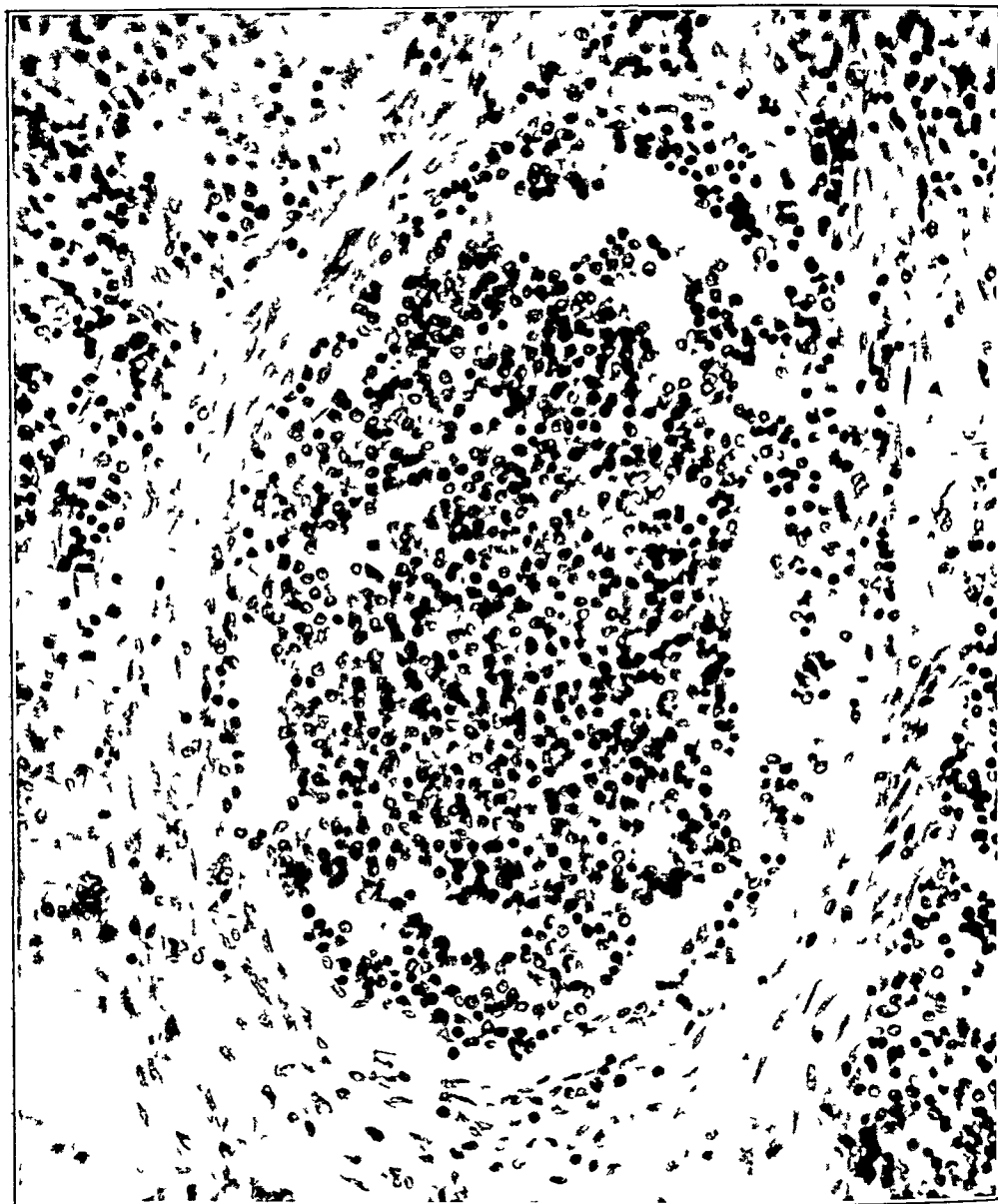


Fig 4—Primary carcinoma of the lungs, showing thrombosis of a pulmonary vein by tumor and tumor cells infiltrating the vascular wall which has ruptured in one area (upper part) A small celled, bronchogenic cancer

Besides the chemical composition of the brain invoked by Lubarsch to explain the success of the metastatic growth, there is, I think, another factor—the anatomic and physiologic condition that plays the outstanding rôle and is indeed more favorable (for the growth) in the brain than in the lungs. In bronchogenic cancers, there occurs, as a rule, a more

or less extensive atelectasis of the healthy part of the involved lung, accompanied by wide necrosis of the tumor itself, interfering undoubtedly with the advance of the growth. In the brain, however, the tumor is provided with an excellent blood supply—a primordial factor indispensable for the growth of tissues in physiologic, as well as in pathologic, conditions. Moreover, Ewing³² affirms that there is, as a rule, an increased anaplasia and more rapid growth in metastatic tumors in general.

The five case histories which follow have a twofold interest. In the first place, in all of them the complaints were referred to the cerebral metastases, and the primary pulmonary tumor either was accidentally found following an operation for removal of the metastatic tumor or was a postmortem surprise. In the second place, in the presence of such a double lesion with dominating intracranial symptoms, should a surgical attempt be made to remove the cerebral lesion? This has been recently discussed by Grant³³ from the Surgical Clinic of the Peter Bent Brigham Hospital.

CASE 8—An adult with acute psychosis classed as an intracranial tumor suspect. Death without operation. Necropsy. Primary carcinoma of the lungs with generalized metastases to the brain, leptomeninges, suprarenals, liver and lymph nodes.

History—A man, aged 55, entered the hospital, Oct. 23, 1921, complaining of severe headaches, tinnitus of the left ear, unsteadiness of gait, projectile vomiting, difficulty in talking, hallucinations and Bell's palsy. He had always been healthy up to September, 1921. The family history was negative.

The present illness began suddenly on Sept. 20, 1921, when the patient was brought home from work with a paralysis of the left side of the face. At the same time he was disoriented as to time, place and person for a few minutes. Since that time he had been restless and wandering mentally, and his speech had been thick and hard to understand. A few days later he developed projectile vomiting and hallucinations of death.

Physical examination showed an emaciated and disoriented man. The objective symptoms may be summarized as follows: 1. Restlessness and inability to cooperate. 2. Bilateral blurring of the nasal margins of the disks. 3. Protrusion of the tongue slightly to the left. 4. Blood pressure, systolic, 160, diastolic, 80. 5. Eleven cells in the spinal fluid. The fluid was positive for sugar and negative for globulin. In addition to these positive features, the blood Wassermann reaction was negative, the hemoglobin was 90 per cent, and the leukocyte count was 7,800 per cubic millimeter. The temperature was normal. Roentgen-ray examination of the head and sinuses did not show any abnormalities. The patient died after sixteen days in the hospital.

The impression was that possibly an alcoholic psychosis was present.

At necropsy, the primary tumor was found to occupy the entire lower lobe of the left lung. In the brain, metastases were found in the floor of the fourth ventricle on the right, in the lateral ventricle on the surface of the caudate nucleus, beneath the cortex and at the inferior and lateral aspect of the tip of the occipital lobe, in the center of the temporal lobe, and in the leptomeninges.

32 Ewing, J. Neoplastic Diseases, ed. 2-d., 1922, p. 86.

33 Grant, F. C. Concerning Intracranial Malignant Metastases, *Ann. Surg.* 84: 635, 1926.

The features of remarkable interest in this case were the absence of any complaints referable to the respiratory organs, the sudden onset of the disease with cerebral symptoms and the unusually extensive metastases (brain, multiple—leptomeninges, pleura, liver, suprarenals and lymph nodes) It is obvious that the physical signs in the chest had been overlooked on account of the patient's cerebral condition

CASE 9—A woman with a six months' history of headaches, regarded as a cerebral tumor suspect Operation with removal of tumor from left occipital lobe Recovery Pathologic diagnosis Carcinoma metastatic from the lungs

History—A Jewish housewife, aged 46, was admitted to the hospital, April 6, 1925, complaining of headaches She had been healthy up to about five months previously, when she began to have frontal headaches which were at first mild, but which later became severe and continuous, confining her to bed Her



Fig 5 (case 9) —Primary carcinoma of the lungs A well circumscribed tumor originating in the bronchus of the right hilum

bowels, which always had been regular, became obstinately constipated, requiring daily cathartics or enemas Her appetite was good, but she had lost 21 pounds (9.5 Kg) in weight since the onset of the disease

Examination of the viscera showed nothing of importance Clinically, no pathologic changes were present

A neurologic examination showed slight weakness of the right side of the face, and a coarse tremor of the tongue The reflexes were normal

A lumbar puncture showed clear fluid which was under normal pressure There were only lymphocytes in the fluid (45 before and 30 after hemolysis) The eyegrounds showed bilateral choked disks with hemorrhages

The impression was that a tumor of the left side of the brain or pachymeningitis hemorrhagica was present

The patient was operated on, and a cystic tumor as large as a hen's egg was found situated in the left occipital lobe On histologic examination, the tumor was composed of squamous epithelial cells arranged in tubules and wide strands

The pathologic diagnosis was metastatic carcinoma

Roentgenologic examination showed a rounded mass in the hilum of the left lung having fairly sharp edges and being approximately 5 cm in diameter (fig 5)

The patient was discharged without pulmonary or cerebral symptoms five weeks after the operation (about seven weeks after admission). The diagnosis was primary carcinoma of the left bronchus with metastases to the brain.

There are analogies between this case and case 8. 1. There were no complaints referable to the organs of the chest in either. 2. In both cases the cerebral symptoms were the leit motif of the patients' complaints. It will be noted, however, that in case 8, the onset of the disease was sudden and stormy, and the cerebral lesion unlocalizable. In case 9 the onset was insidious, and the clinical picture was that of a tumor of the brain.



Fig 6 (case 10)—Primary carcinoma of the lungs. Roentgenogram taken about six months after the onset of the cerebral symptoms.

CASE 10—A man with a four months' history of right sided paralysis, loss of speech and headache. Cerebral tumor suspect. Operation with removal of tumor from left temporal region. Pathologic diagnosis: Carcinoma, metastatic from the lungs.

*History—*An American born merchant, aged 56, whose past and family histories were negative, was admitted to the clinic, June 25, 1925, with paralysis of the right side, loss of speech and headache. He was apparently well until March 8, 1925, when he suddenly began to have attacks of twitching of the right side of the face with slight difficulty in closing his mouth, and slight difficulty in speech. Four days later, he had three such attacks, each one beginning with convulsive movements of the right side of the face, associated with disturbances in speech and paralysis of the right side of the face. His condition was progressing, and the diagnosis of tumor of the brain was made. A cerebral exploration without a subtemporal decompression was performed on March 26. No tumor

was found. He had an uneventful recovery, but his symptoms increased steadily, speech becoming much worse, his arm becoming paralyzed, and his leg becoming involved. He was given a few deep roentgen-ray treatments, with temporary relief.

The patient was well developed and well nourished. The positive symptoms can be summarized as follows: 1 The patient was in a semicomatose condition, he was incontinent and fairly responsive to strong stimulation. 2 Right-sided spastic hemiplegia with increased reflexes, bilateral ankle clonus and Babinski sign on the right were present. 3 Bilateral choked disks with hemorrhages, with formation of new tissue and exudate were also present.

The impression was that a cerebral tumor, probably in the left temporal region, was present.

The patient was operated on, June 27, 1925, and a massive, partly degenerated tumor was removed, which on histologic examination was composed of epithelial cells having a tubular arrangement. The diagnosis of a metastatic carcinoma was then made, and it was suggested that the tumor originated in the lungs.

On July 21, 1925, roentgen-ray examination of the chest showed a well circumscribed, large rounded mass in the left upper lobe anteriorly, extending from the first to the third ribs (fig 6). The remaining lung fields were essentially normal. The impression of the roentgenologist was that a tumor of the lung was present.

On July 28, 1925, the patient had made an excellent recovery, and all his symptoms had improved considerably. He was discharged with the diagnosis of primary carcinoma of the lungs, metastatic to the brain.

This case is, to a certain extent, an intermediary between cases 8 and 9. Similar to case 8, the onset was sudden and stormy, but the cerebral lesion was difficult of localization. It was thought at first that there might be a cerebral vascular lesion of some kind. Its analogy with case 9 lay in the progressiveness, so to say, of the clinical course, this finally gave the definite picture of a tumor of the brain, which was followed by cerebral exploration.

CASE 11—A woman with a history of headaches accompanied by nausea and vomiting of five months' duration. Intracranial tumor suspect. Operation with removal of tumor. Death. Necropsy. Carcinoma, metastatic from lungs.

History—A. M. W., a trained nurse, aged 48, with a negative family history, was admitted to the hospital, Dec. 15, 1913, complaining of headaches. The past history, except for asthma of long duration, was unimportant. The onset of the present illness had been insidious. In February, 1913, she began to feel tired, although she worked without great discomfort. About September, 1913, she had an attack of severe headache, accompanied by nausea and vomiting, and required morphia for relief. Since that time similar attacks had occurred several times a week, usually being frontal, and drugs gave little relief.

Examination showed the patient to be fairly well developed and nourished, with no evidence of acute illness. The positive symptoms can be summarized as follows: Extreme degree of choked disk, protrusion of the tongue to the right, aphasia, ataxia and exaggerated deep reflexes, failing memory, poor concentration and marked depression. An examination of the visceral organs showed nothing of importance.

On Jan. 13, 1914, a tumor about the size of a hen's egg was removed from the right frontal lobe. The patient died about forty-eight hours following the operation.

Necropsy—All parts of the brain were literally studded with tumor nodules of varying size. In the brain, more in the gray than in the white substance, were innumerable small foci, the diameters of which ranged in size from that of a

pinpoint to 2 cm, they were filled with a clear, gelatinous substance, often coalescing. These small foci were in all sections of the brain, but in some places were much more numerous than in others. The groupings of these nodules had some resemblance to grouping of tubercles in hematogenous tuberculosis, possibly corresponding to the distribution of arterial branches.

Microscopically, the tumor was composed of columnar cells having in areas an adenomatous arrangement, and in others having a tendency to form cysts. In one section from the hippocampus, a tumor metastasis was found within the vessels. In another, a vessel was actually lined with the tumor cells with blood inside of it. Often the cells seemed to grow on the wall of the vessel itself.

From a clinical standpoint, this case closely resembles case 9 because of the insidious onset of the cerebral symptoms, by the patient's complaint, and by the positive symptoms. Additional information received from a clinic in which the patient was previously under treatment was of interest. From this report it was clear that the patient had had thoracic disturbances during three months previous to her admission to the hospital. The heart was displaced to the right, the apex beat being felt 2.5 cm. to the right from the mammillary line.

In this case also the neurologic signs and symptoms had overshadowed those of the chest.

CASE 12—A man, aged 41, with a six months' history of right-sided paralysis, loss of speech and severe headaches. Operation with removal of tumor. Result: Improvement. Pathologic diagnosis: Carcinoma, metastatic from the lungs.

*History—*A farmer, a native of Virginia, aged 41, with a negative past and family history, was admitted to the hospital, May 31, 1920, with paralysis of the right side of the body, inability to speak, severe headache and slight nausea and vomiting. He had had diphtheria at the age of 13, followed by slight hoarseness, and measles, mumps and chickenpox with complete recovery. He had always been well except for influenza in 1919 followed by a prolonged cough. It was thought that he had pulmonary tuberculosis, but this was not confirmed by a specialist.

The present illness began in December, 1919, when he noted weakness of the right foot and about three weeks later, weakness of the right hand. This gradually increased until the whole right side was affected. Two months later (in February, 1920) he began to have projectile vomiting. The diagnosis of a tumor of the brain was made, a subtemporal decompression performed, but no tumor was disclosed. Following operation, the patient had a flaccid paralysis of the right side including the face.

Physical examination showed a poorly developed and poorly nourished man, partially paralyzed on the right side but able to walk with assistance. He had a marked motor and sensory aphasia, flaccid paralysis of the whole right side with increased reflexes, a right facial paralysis not involving the brow, and impaired sensation of the whole right side. The diagnosis of a tumor of the brain was made again, and an operation was performed, June 9, 1920. Portions of a necrotic and infiltrating tumor were removed, which on histologic examination proved to be a carcinoma. The patient remained in the hospital twenty-eight days and was discharged improved.

On July 26, roentgen-ray examination showed the chest to be asymmetrical. The mediastinum was displaced toward the left, and there was considerable increase in the density of the shadows about the left hilum, with some clouding of the posterior mediastinum at the level of the tracheal bifurcation. The right side of the chest was distinctly larger than the left. The increased infiltration about the hilum of the lung was, according to the roentgenologist, compatible with a mediastinal tumor.

Clinically, this case was a counterpart of cases 9, 10 and 11. It is of interest in that it showed an asymmetry of the chest, the side affected being smaller. This was discussed in connection with case 5.

COMMENT

As a pathologic entity, primary carcinoma of the lungs does not possess any outstanding peculiarities not proper to carcinoma elsewhere in the body. Viewed from this angle, it therefore ought to be regarded as a part of the entire problem of malignant disease.

From a clinical standpoint, as with visceral cancers in general, the patient ignores the early symptoms of the disease. Moreover, it is possible that in the early stages, and it is not known how long they are, the lesion runs an entirely silent course. A pulmonary tumor, when disclosed, is usually found accidentally at a routine roentgenologic examination, at necropsy, or, as in some of the cases reported, during a surgical intervention for the removal of a metastatic cerebral lesion. A clinical diagnosis of this condition, based on a few adventitious thoracic signs, found at this early stage of the disease is therefore out of the question.

As a rule, the patient consults the physician when the growth is well advanced. Here, the failure in making a prompt diagnosis is due, in the first place, to the similarities existing between this condition and a number of other chronic pulmonary diseases, in the second place, to the fact that one is actually perplexed with the "clinical irregularity" and the amazing disproportion between the physical signs and the patients' symptoms. It is still believed that symptoms and signs reflect precisely the underlying anatomopathologic lesion. This may be true in acute pulmonary conditions, but in cancer of the lung the localization of the tumor and the mode of its advance lead oftentimes to ambiguous signs confusing the most skilful clinician (cases 1, 2 and 3). At this advanced period of the disease, then, a diagnosis is based rather on the "atypical features" of the clinical picture, or it is made by exclusion. (A few valuable signs found on physical examination of the chest in a certain type of tumor have been described by Fishberg³⁴ in a recent report.)

In brief, it appears that there are no clinical signs which, taken alone, would make the diagnosis of a primary neoplasm of the lung certain. It is believed that the roentgen-ray examination of the chest, bronchoscopy, and the intrapulmonary injection of iodized oil 40 per cent used separately or in combination, when added to the clinical data, make the diagnosis of this disease reasonably certain.

³⁴ Fishberg, Maurice. Diagnosis of Pulmonary Neoplasm, *Arch Int Med* 37:445 (June) 1926.

CONCLUSIONS

1 European statistics are to the effect that the incidence of primary carcinoma of the lungs in relation to epithelial malignant disease in general is disproportionately high, figures given indicate that it occurs there in from 5 to 6 per cent of all post mortems. In this country, similarly, an increase in the occurrence of primary carcinoma of the lungs has been noted in the last decade.

2 Primary carcinoma of the lungs owes its statistical increase to (a) better diagnostic methods and (b) increased human longevity. The increase, therefore, is more apparent than real.

3 A diagnosis of primary carcinoma of the lungs based on physical signs alone is never certain. Careful analysis of physical signs, combined with clinical observation and laboratory methods of investigation (roentgen rays, injection of iodized oil and bronchoscopy), makes the diagnosis of primary carcinoma of the lungs reasonably certain. Bronchoscopy, with removal of the tissue, is apparently the most reliable criterion.

4 The wide distribution of metastases in primary carcinoma of the lungs is due to (a) peculiarities of its structure, i. e., it is frequently soft and abundantly cellular, and (b) its slow growth, since rapidly growing tumors usually cause death of the patient long before metastases have time to develop.

5 The frequent occurrence of cerebral metastases from primary pulmonary cancer, as compared with cancers from elsewhere in the body, is due to the absence of a barrier between the lungs and the brain. Metastases from elsewhere in the body on their way to the central nervous system pass primarily through the "sieve" of the lungs, in which they are usually "immured" and not infrequently perish.

6 Metastases to the brain from a primary pulmonary cancer are, as a rule, hematogenous in character.

CHANGES IN THE KIDNEY IN ANIMALS WITH INCREASED BLOOD PRESSURES WHILE ON HIGH PROTEIN DIETS*

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This paper is concerned with the changes found in the kidneys of three groups of rabbits that had been fed high protein diets for periods as long as twenty-four months. Many of the animals developed an increased blood pressure and clinical evidence of kidney injury¹. This evidence consisted first of albumin and casts in the urine, later of an increase of the nonprotein nitrogen and urea nitrogen of the blood and finally of a decrease of carbon dioxide of the blood plasma.

The routine procedure in experiments were as follows

Forty-eight carefully selected young rabbits were placed in individual metabolism cages. None of these animals had a spontaneous nephritis or a systolic blood pressure higher than 74 of mercury. The cages were kept out doors the year around. The blood pressures were obtained once each month by a method previously described². At monthly intervals also, twenty-four hour samples of the urine were collected for p_H determinations, and single specimens were obtained by pressure over the bladder, or by catheterization, for chemical and microscopic study. Once each month enough blood was withdrawn from the marginal ear vein to determine the nonprotein nitrogen, the urea nitrogen and the carbon dioxide of the blood plasma. The methods of Folin and Wu³ were used for the nitrogen determinations, and the method of Van Slyke and Cullen⁴ for the carbon dioxide per cent by volume of the blood plasma. Monthly weight charts were kept. The special diets were given in such quantity that uneaten food was constantly present. Water was likewise provided ad libidum.

At the conclusion of the experiments the animals were killed by a blow on the neck. Sections of the various tissues were placed in 10 per cent formaldehyde and in Zenker's fluid. They were sectioned by the paraffin method, and stained with hematoxylin and eosin.

* From the Santa Barbara Cottage Hospital

1 Nuzum, F R, Osborne, Margaret, and Sansum, W D. The Experimental Production of Hypertension, *Arch Int Med* **35** 492 (April) 1925

2 Nuzum, F R, Seegal, Beatrice, Garland, Ruth, and Osborne, Margaret. Arteriosclerosis and Increased Blood Pressure, Experimental Production, *Arch Int Med* **37** 733 (June) 1926

3 Folin, O F, and Wu, H. A System of Blood Analysis, *J Biol Chem* **38** 81, 1919

4 Van Slyke, W D, and Cullen, G E. The Bicarbonate Concentration of the Blood Plasma, Its Significance, and Its Determination as a Measure for Acidosis, *J Biol Chem* **30** 289, 1917

Newburg and Clarkson⁵ fed high protein (26.8 to 36.2) diets to rabbits for from six to nine months. They found changes in the tubular epithelial cells of the kidneys, consisting of granulation, vacuolization, desquamation and flattening, with a resulting dilatation of the tubules. The glomeruli were not changed. Fibrosis was absent. The evidence at hand led them to believe that the kidney injury was caused either by excessive excretion of amino-acids or in part by the acid character of the urine. They did not believe that the latter factor alone was responsible.

Polvogt, McCollum and Simonds⁶ gave rats diets ranging in protein content from 21 to 41.3 per cent for periods of from 250 to 400 days. These diets were "defective only in that they contained excessive amounts of protein." The kidneys were found to be large and congested, and the capillaries much distended. Hyaline material was found between the glomerular tufts and Bowman's capsule. The tubular epithelium was degenerated. In short "all the rats fed the diets high in protein had lesions of the kidneys—of considerable severity."

Newton Evans and Risley⁷ gave 75 per cent casein, 58 per cent rabbit meat, 44 per cent wheat gluten and 39 per cent soy bean protein diets to four groups of rats for periods varying from seven to fifteen months. Clinical evidence of nephritis was present in the urine. Marked tubular degeneration was found in the kidneys, together with thickening of Bowman's capsule, hyaline compression of the tufts, extensive round cell infiltration and repeated instances of definite replacement of renal parenchyma by connective tissue. These investigators are the only ones to report definite evidence of connective tissue increase.

On the contrary, other investigators report negative results following high protein feeding experiments.

Drummond, Crowder and Hill⁸ fed young growing rats a high protein (caseinogen) diet for 100 days. Kittens were fed a high protein (raw beef) diet for 120 days. Changes were not found in the kidneys of either species.

Anderson⁹ gave a 30.5 per cent beef protein diet for "about a year" to rabbits that had been partially nephrectomized. Only hypertrophy of the remaining portion of the kidney was found.

5 Newburgh, L. H., and Clarkson, Sarah. Renal Injury Produced in Rabbits by Diets Containing Meat, *Arch Int Med* **32** 850 (Dec.) 1923.

6 Polvogt, L. M., McCollum, E. V., and Simmonds, Nina. The Production of Kidney Lesions in Rats by Diets Defective Only in that They Contain Excessive Amounts of Protein, *Bull Johns Hopkins Hosp* **34** 168, 1923.

7 Evans, N., and Risley, E. H. High Protein Ration as a Cause of Nephritis, *California & West Med* **23** 437, 1925.

8 Drummond, J. C., Crowder, G. P., and Hill, E. L. G. Nutrition on High Protein Diets, *J Physiol* **56** 413, 1922.

9 Anderson, Hilding. Experimental Renal Insufficiency, *Arch Int Med* **37** 313 (March) 1923.

Jackson and Riggs¹⁰ gave a 76 per cent casein diet to five rats and a similar diet, with sodium bicarbonate added, to three rats for periods varying from ten to twenty months. They obtained only hypertrophy of the kidneys.

Osborne and Mendel¹¹ gave a meat residue diet (50 and 55) to growing rats for eighty days. The kidneys of these animals averaged twice the weight of normal rat kidneys, and were one-third greater in size. They did not find any changes of an inflammatory or degenerative nature.

There is a sharp contrast between the results found in these reports. In three of the four instances in which hypertrophy alone was obtained, the duration of the experiments varied from 80 to 100 days. In the instance in which other changes were found in the kidneys, the diets were continued from 250 to 450 days. The longer time interval resulted in positive results for three of the four groups of investigators here recorded.

As these reports suggest, there is increasing experimental evidence that excessive protein or other disturbances occasioned by such a diet are capable of causing degenerative changes in the kidneys.

Newburgh and Clarkson have advanced the hypothesis that certain of the amino-acids that result from protein breakdown during the processes of digestion are capable of causing increased blood pressure. It is suggested that later this may lead to degenerative changes in the kidneys. Major has demonstrated experimentally that methyl-guanidine, a product of protein metabolism in the body, is capable of producing an elevation of blood pressure. He advances the hypothesis, and likewise suggests this possible relationship to the degenerative kidney changes that follow continued hypertension.

I have attempted to obtain experimental degeneration of the kidneys by feeding high protein diets over long periods. I have been impressed with the recently advanced theory that the passage of excessively acid urines over long intervals of time might in itself be responsible for kidney degeneration. The protein in the diet has an acid ash, and produces an acid urine. The greater the amount of protein in the diet, the more acid the urine.

With this in mind, I have given diets high in protein content but containing the requisites necessary to growth and health to three groups of twelve animals each. A fourth group of twelve animals was kept as controls and fed greens, barley and alfalfa. These experiments

10 Jackson, Henry, and Riggs, Margaret D. The Effect of High Protein Diets on the Kidneys of Rats, *J Biol Chem* **68** 101, 1923.

11 Osborne, T. B., Mendel, L. B., Park, E. A., and Winternitz, M. C. Physiological Effects of Diets Unusually Rich in Protein or Inorganic Salts, *J Biol Chem* **71** 317, 1927.

were continued for twenty-four months (720 days), or approximately one-half of the natural life of a rabbit. One group of animals was given a diet originally suggested by McCollum,⁶ containing liver protein, 20 per cent, casein, 20 per cent, maize, 20 per cent, wheat, 30 per cent, navy beans, 5.5 per cent, cod liver oil, 2 per cent, calcium carbonate, 1.5 per cent, and salt, 1 per cent. Greens were fed at given intervals to prevent the development of deficiency diseases. The urines

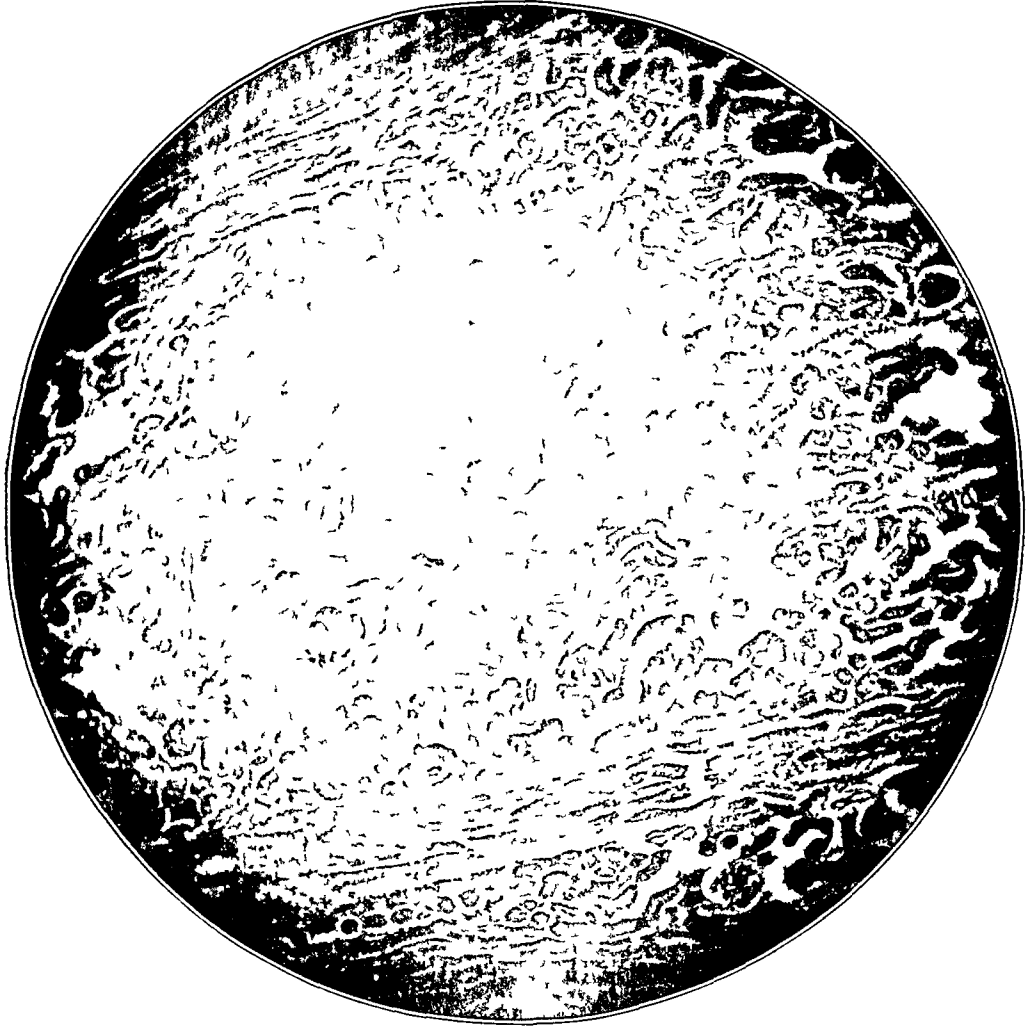


Fig 1—Section through cortex of normal rabbit kidney to be contrasted with sections in figures 2, 3 and 4

from these animals were acid, the p_H ranging from 5 to 6. A second group of twelve animals was given a vegetable protein (16 per cent) diet, the protein being derived from oats. In addition, cod liver oil and tomato were given ad libitum, and alfalfa was included twice a week. The urines of this group were continuously acid, the p_H averaging from 5.5 to 6. A third group was given a third type of vegetable protein (38 per cent) diet, this protein being derived from soy beans, cod liver oil, tomato and alfalfa were also given as stated previously

TABLE 1—*Pathologic Changes in Kidneys of Animals on Liver Diet*

No of Rabbit	Maximum			Urine		Duration of Experiment	Cause of Death	Kidney Changes
	Maximum Blood Pressure	Minimum Carbon Dioxide	Nonprotein Nitrogen	Reaction	Albumin			
39	108	50.0	60.0	Acid, pH 5.5	++ hyaline and granular casts	11 mo	Killed	Round cell infiltration, increased cellularity of the capillary tufts, thickening of the walls of the vessels in the medullary rays, hyaline material compressing the glomeruli
42	100	48.0	50.0	Acid, pH 5.8	++ hyaline and granular casts	10 mo	Broncho pneumonia	Round cell infiltration, thickening of Bowman's capsule, diffuse areas of fibrosis, increased cellularity of the capillary tufts, thickening of the walls of the vessel in the medullary rays
44	97	50.0	47.0	Acid, pH 5.5	++ granular and leukocytic casts	10 mo	Broncho pneumonia	Tube casts, slight diffuse areas of fibrosis, increased cellularity of the capillary tufts, thickening of the walls of the vessels in the medullary rays
43	87	45.0	49.6	Acid	++ granular casts	5 mo	Broncho pneumonia	Round cell infiltration, tube casts
40	83	50.0	54.6	Acid	++ granular casts	4 mo	Broncho pneumonia	Cloudy swelling of the cells lining the convoluted tubules, round cell infiltration, increased cellularity of the capillary tufts
38	79	42.0	42.6	Acid	Trace	3 mo	Broncho pneumonia	Cloudy swelling of the cells lining the convoluted tubules round cell infiltration, increased cellularity of the glomeruli
45	85	51.9	42.3	Acid	—	3 mo	Broncho pneumonia	No change
36	95	48.1	42.3	Acid	—	3 mo	Broncho pneumonia	Round cell infiltration, tube casts, hyaline material compressing glomeruli
46	76	49.0	60.0	Alkaline	Trace	2 mo	Broncho pneumonia	Round cell infiltration, tube casts, cloudy swelling of the cells lining the convoluted tubules, adherent glomeruli

This diet gave an alkaline urine with a p_H of 9. The blood pressures in these groups became elevated in from three to four months, and continued so throughout the duration of the experiments, which in many instances were carried on for twenty-four months. There was evidence of kidney damage in each of these three groups, as shown by the presence of albumin in the urine, the frequent presence of casts and an increase of the nonprotein nitrogen and urea nitrogen of the blood. In

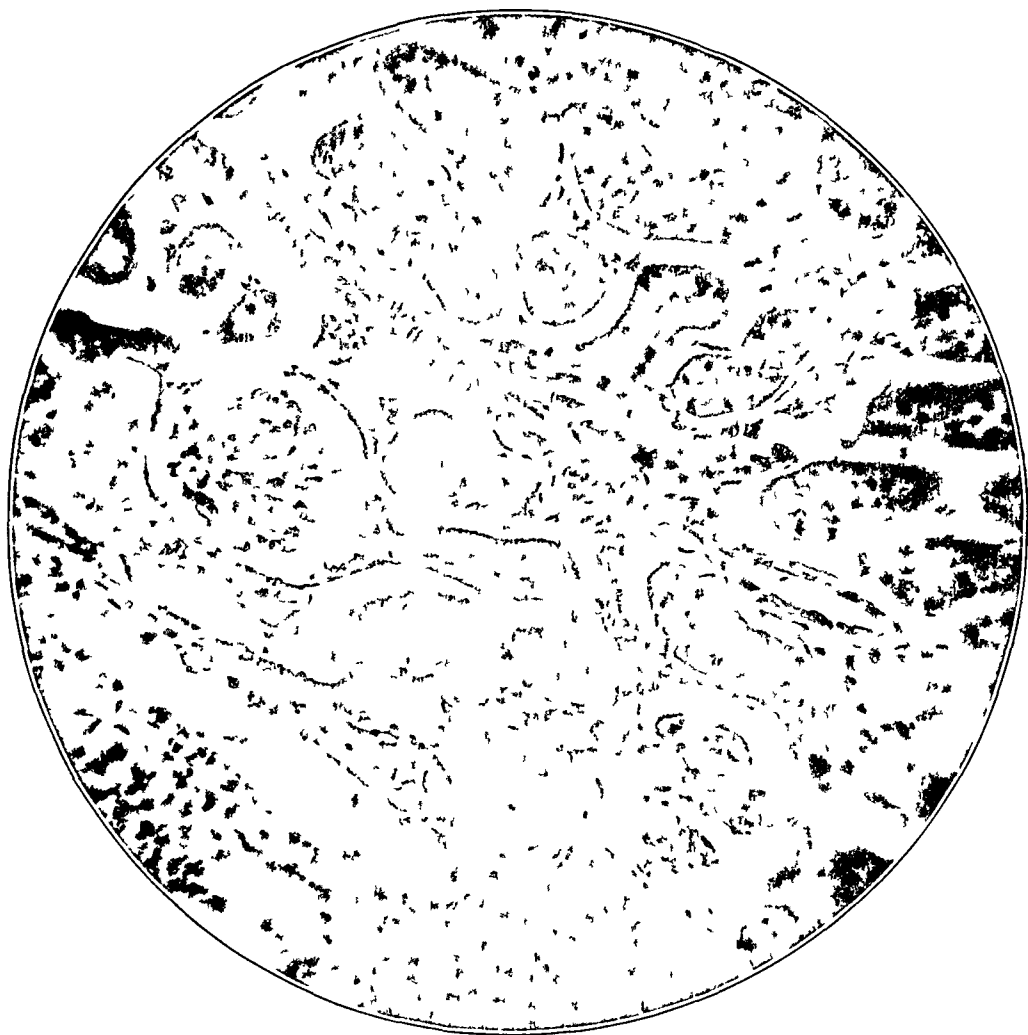


Fig 2—Thickening of walls of a small artery leading to two glomeruli, this thickening makes the vessel stand out distinctly in contrast to normal vessels in the kidney cortex

many instances there was a marked reduction of carbon dioxide of the blood plasma

A pathologic study of the kidneys of these four groups of animals was undertaken to determine what type of change had occurred, and whether these changes were more marked in the animals with excessively acid urine

A greater degree of kidney damage, as determined by chemical studies of the urine and blood, was apparent in the animals that devel-

TABLE 2—*Pathologic Changes in Kidneys of Animals on Gram Diet*

No of Rabbit	Maximum		Minimum		Urine		Duration of Experiment	Cause of Death	Kidney Changes
	Maximum Blood Pressure	Nonprotein Nitrogen	Carbon Dioxide	Urea Nitrogen	Reaction	Albumin			
11	100	60.0	42.0	33.0	Acid, pH 5.3	++ granular casts	23 mo	Killed	Tube casts
1	90	53.1	45.0	23.1	Acid, pH 5.5	++ granular casts	23 mo	Killed	Round cell infiltration, dilatation of tubules, increased number of epithelial cells in the glomeruli
3	95	57.0	47.0	38.0	Acid	+ hyaline and granular casts	23 mo	Killed	Round cell infiltration, diffuse dilatation of the tubules
5	94	53.0	45.0	32.9	Acid, pH 5.9	+ hyaline and granular casts	23 mo	Killed	Tube casts
8	98	64.0	48.0	40.0	Acid, pH 5.4	++ hyaline and granular casts	23 mo	Killed	Hyaline material compressing tufts, thickening of the vessel- in the medullary ray
6	97	54.1	43.0	28.0	Acid, pH 6.2	+	22 mo	Killed	Round cell infiltration, scattered areas of fibrosis, diffuse dilatation of tubules, increased cellularity of the glomeruli, thickening of the walls of the vessels in the medullary rays
2	90	48.0	45.0	25.0	Acid, pH 6.4	+ granular casts	22 mo	Killed	Diffuse dilatation of the tubules, increased cellularity of the glomeruli
10	88	46.2	44.0	25.0	Acid	+ hyaline and granular casts	13 mo	Broncho pneumonia	Round cell infiltration, diffuse dilatation of the tubules, thickening of the vessels in the medullary rays, tube casts
7	90	46.0	48.0	20.0	Acid	Trace, granular casts	13 mo	Broncho pneumonia	Round cell infiltration, thickening of Bowman's capsule and of the walls of the vessels in the medullary rays
4	100	60.0	53.8	39.0	Acid	++	7 mo	Broncho pneumonia	No change
12	90	58.8	51.0	35.7	Acid	Trace, granular casts	7 mo	Broncho pneumonia	Diffuse dilatation of the tubules, increased cellularity of the glomeruli, thickening of the vessel walls in the medullary rays
9	80	56.0	48.8	28.0	Acid	—	5 mo	Broncho pneumonia	No change

oped a more marked increase in blood pressure. A considerable degree of arteriosclerosis was also present in the aorta and in the coronary arteries of many of these animals. These changes were found in the kidneys of the rabbits on the liver diet. This diet gave the most acid urines. Five of nine animals that were on this diet for four months or longer presented diffuse dilatation of the tubules. This dilatation was due in part to a flattening of the cells lining the first and second

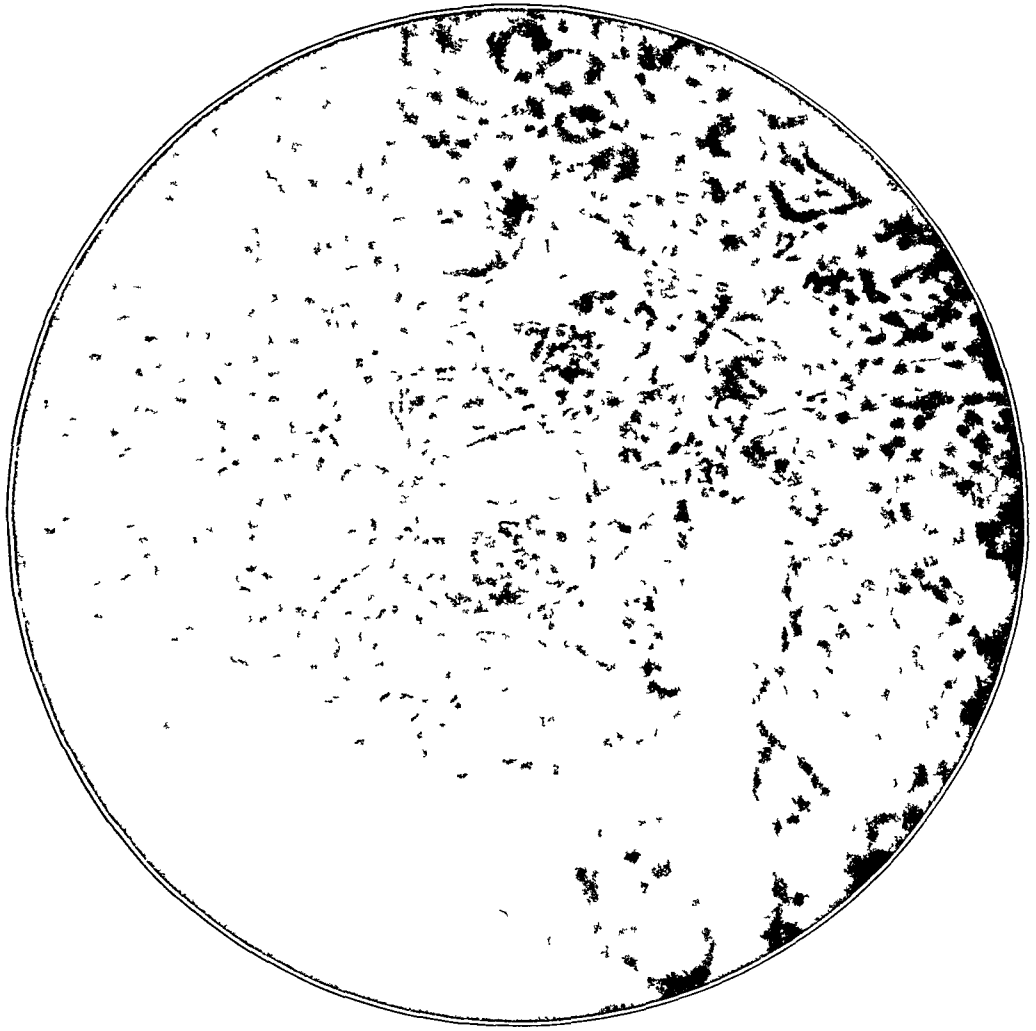


Fig. 3—Compression of glomerular tuft with hyaline exudate, atrophy of cells lining convoluted tubules with dilatation of tubules, thickening of glomerular tuft

portions of the convoluted tubules. Scattered areas of round celled infiltration were present in all these instances. Numerous tube casts were found. Six of the animals presented a marked increase in the cellularity of the capillary tufts in the glomeruli. In addition, five of these six presented a thickening of the walls of the vessels in the medullary rays. Six of the animals presented further diffuse areas of sclerosis scattered throughout the cortex. This sclerosis consisted of a thickening of Bowman's capsule and of a definite increase of fibrous connective tissue cells between the convoluted tubules.

TABLE 3—*Pathologic Changes in Kidneys of Animals on Gram Diet*

No of Rabbit	Maximum				Urin		Duration of Experiment	Cause of Death	Kidney Changes
	Maximum Blood Pressure	Minimum Carbon Dioxide	Nonprotein Nitrogen	Urea Nitrogen	Reaction	Albumin			
13	90	57.0	70.0	42.9	Alkaline, pH 7.3	++ granular casts	22 mo	Broncho pneumonia	Cloudy swelling of the cells of convoluted tubules
16	84	66.0	75.0	42.9	Alkaline, pH 8.4	++ granular and hyaline casts	21 mo	Broncho pneumonia	Tube casts, diffuse dilatation of the tubules, marked increase in the cellularity of the glomeruli
18	90	67.0	60.0	42.0	Alkaline, pH 8.8	++	21 mo	Killed	No change
27	90	67.0	65.0	46.0	Alkaline	++	20 mo	Ulcerative enteritis	Round cell infiltration, atrophy and dilatation of the tubules, thickening of the walls of the capillary tufts, diffuse areas of fibrosis
17	90	63.0	90.0	60.0	Alkaline	+ granular and hyaline casts	17 mo	Broncho pneumonia	Round cell infiltration, atrophy and dilatation of the tubules, diffuse areas of fibrosis
26	90	59.8	65.9	50.0	Alkaline	—	16 mo	Infection from bite wound sustained 1 month before death	Round cell infiltration, tube casts, atrophy and dilatation of the tubules, scattered areas of fibrosis, thickening of Bowman's capsule and of the vessels of the glomerular tufts
25	89	58.6	60.0	31.0	Alkaline	Trace	13 mo	Broncho pneumonia	Round cell infiltration, increased cellularity of the glomerular tufts
15	83	51.9	57.7	33.0	Alkaline	—	10 mo	Killed	Round cell infiltration, increased cellularity of the glomerular tufts, thickening of Bowman's capsule, diffuse dilatation of the tubules
28	87	57.0	49.5	25.0	Alkaline	Trace	9 mo	Broncho pneumonia	Cloudy swelling of the cells lining the convoluted tubules, diffuse dilatation of the tubules, thickening of Bowman's capsule, increased connective tissue in the medullary rays
14	70	45.0	52.2	28.9	Neutral	++ granular and hyaline casts	8 mo	Broncho pneumonia	Cloudy swelling of the cells lining the convoluted tubules, diffuse dilatation of the tubules, round cell infiltration, increased cellularity of the tufts, thickening of Bowman's capsule

The group on the grain diet, in which the urines were also acid, although as a rule less so, exhibited changes of a similar character, but they were not so marked. In this group, round cell infiltration was present in five of twelve instances. Tube casts were occasionally found. Diffuse dilatation of the tubules was present in six of twelve instances. Thickening of the vessel walls in the medullary rays was found five times. An increased cellularity of the glomerular tufts was observed

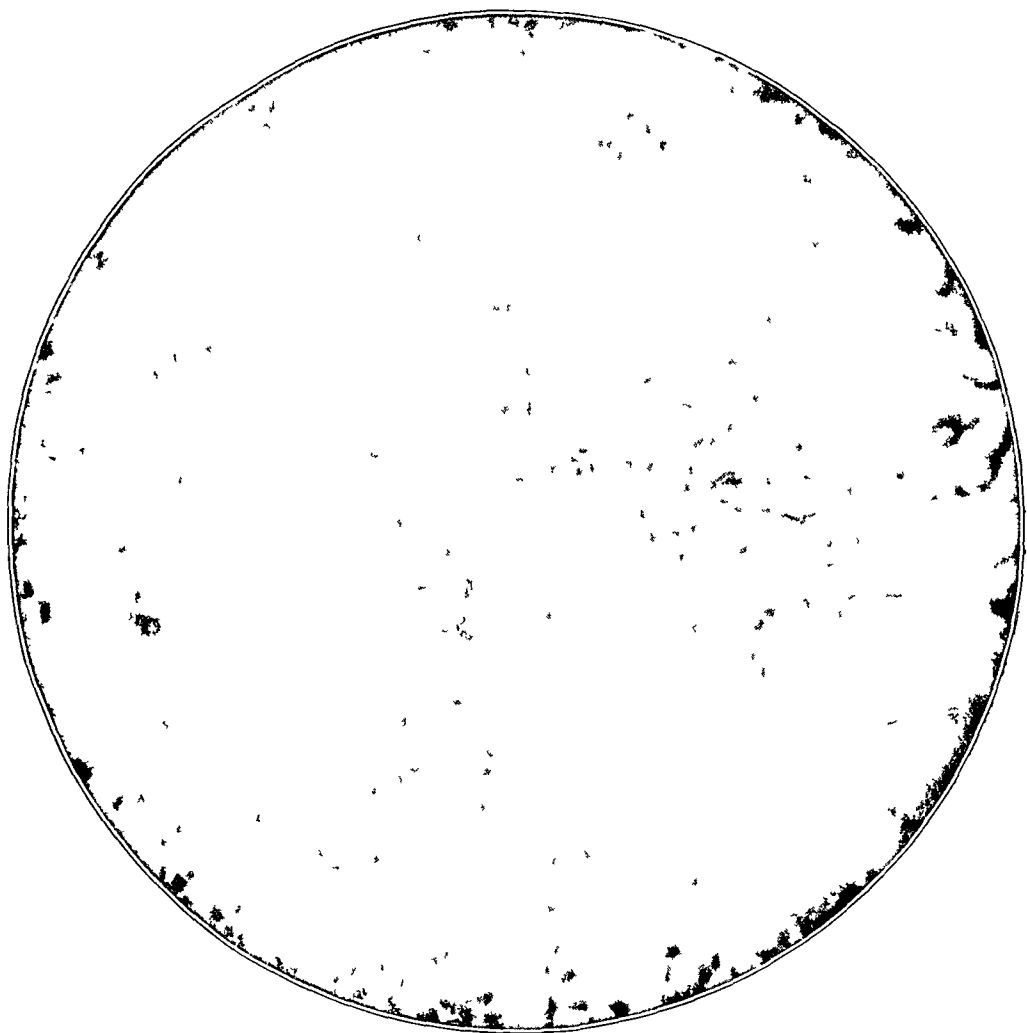


Fig. 4—Further marked compression of glomerulus with hyaline material and changes as recorded in figure 3

in four instances. In one instance the tuft was compressed by hyaline exudate within Bowman's capsule. The kidneys of three of the twelve animals did not present any change.

In the soy bean group the urines were excessively alkaline, the p_H averaging 9. Two of ten animals on this diet for four months or longer presented kidneys in which changes were not found. Diffuse dilatation of the convoluted tubules and scattered areas of round celled infiltration were present in eight instances. Increased cellularity of the

glomerular tufts was noted six times. Distinct thickening of Bowman's capsule was present in three instances.

In the group of control animals, abnormal changes were not noted in seven of twelve instances. Three animals presented a few scattered areas of round cell infiltration in the cortex. Cloudy swelling of the cells lining the convoluted tubules was present once. Focal atrophy of the tubules was present once. A localized area of fibrosis of the cortex has been reported in widely varying percentages in the kidneys of rabbits which were being studied histologically for the presence of spontaneous nephritis.

COMMENT

The characteristic changes in the kidneys of rabbits fed for many months on diets high in protein were found to consist of dilatation of the convoluted tubules, flattening and vacuolization of the cells lining these tubules, scattered areas of round cell infiltration, a marked increase in the cellularity of the capillary tufts of the glomeruli, a thickening of the walls of the vessels in the medullary rays and a thickening of Bowman's capsule. Before the animals were killed and the organs obtained for study, the urine had repeatedly shown the presence of albumin and casts. The blood had shown an increase in nonprotein nitrogen and urea nitrogen, and the blood pressures were increased.

The type of tubular dilatation and the changes in the cells lining the tubules, as described, had also been carefully described by Newburgh and Clarkson⁵ and is considered by them a result of high protein diets. They did not, however, find evidence of glomerular injury or of any increase of connective tissues. I found evidence of thickening of the walls of the vessels in the medullary rays and of the capillary tufts of many of the glomeruli. The thickening consisted of a definite increase of cells within the delicate walls of these vessels. The number of nuclei within the glomerular tufts was increased. The change was widely scattered throughout the kidney and did not involve localized areas. There was also an increase of fibrous connective tissue between the tubules. This increase was not like the focal scars found scattered through the cortex of kidneys which are otherwise normal. It was widespread and was found only in those instances that presented atrophy and dilatation of the tubules. These kidneys were slightly smaller than the kidneys of the control group. The average weight of the kidneys from the liver fed group was 21.2 Gm. as compared with 22.7 Gm. in the control group.

The reason for the presence of blood vessel change in the kidneys of the animals may be the fact that my experiments extended over a period of twenty-four months, whereas Newburgh and Clarkson's⁵ animals were kept on high protein diets for from six to nine months.

The changes in the terminal vessels of the kidney are interpreted as a sclerosis. Sclerosis, histologically resembling human sclerosis, was found extensively in the aorta and the coronary arteries and their terminal capillaries in these groups of animals on high protein diets.² Such sclerosis was not found in the control group. I believe that the changes in the blood vessels of the kidneys are the same as those described in the aorta and coronary arteries, and that they represent a true blood vessel disease. The animals that presented these changes had increased blood pressures.

The factors in a high protein diet that might be responsible for the increased blood pressure that resulted in these groups, for the intimal sclerosis that was found and for the kidney changes noted are matters on which there is much discussion. Newburgh and Clarkson⁵ grant that kidney change such as they describe may be due to infection acting on a kidney made susceptible to infection by the diet. They are more inclined to the belief that "the injury caused by the diet is either solely attributable to the excessive excretion of some amino acids or in part to the amino acids, and in part to the acid character of the urine." But the acidity of the urine, they feel, is by itself incapable of causing all of the injury attributable to the diet.

I have been particularly concerned with the responsibility of the passage of excessively acid urines over a long period as an aid in the production of the kidney changes I have described. The urines of the control groups of animals had a p_H of 8. The urines of the group on live1 protein were the most acid of any of the groups, the p_H ranging between 5 and 6. This group presented the most marked kidney change. The group on a 16 per cent oat protein diet likewise passed acid urines, the p_H varying from 5.6 to 6. The kidney changes were somewhat less marked in this group. The urines of the group on the soy bean protein diet were excessively alkaline, and the p_H averaged 9, which is high even for a rabbit. The kidney changes in this group were less marked than those in the others. Seven of ten of these animals presented atrophy of the cells lining the tubules, with resulting dilatation. Diffuse areas of fibrosis were found in three instances. Areas of round cell infiltration were found in six. Newburgh and Clarkson found tubular degeneration of this type in animals fed on a similar diet. They concluded that some factor or factors concerned with the protein in this diet must have been responsible for the change. Martin Fischer¹² has demonstrated that excessive alkalinity, as well as acidity, is capable of producing kidney injury. The p_H of the urine of this group of animals averaged 9. It is possible that the excessive alkalinity in this group of experiments might have been responsible for these changes.

12 Fischer, M. H. Edema and Nephritis, *J. Indiana M. A.* **18** 247, 1925

SUMMARY

Kidney changes of a definite type were found in three groups of animals fed on high protein diets for a period of twenty-four months

These changes were not found in a group of animals kept under similar conditions but fed a mixed diet of alfalfa and greens

The urines from the groups fed the liver and oat diets were acid Albumin and casts were found repeatedly The nonprotein nitrogen and urea nitrogen of the blood were increased The carbon dioxide of the blood plasma was decreased The systolic blood pressures were increased The urines from the group kept on a soy bean diet were excessively alkaline Clinical evidences of kidney injury were likewise present

CONCLUSION

It is possible that the changes described were due in part to the excessive acidity or alkalinity of the urines passed by these animals for a period approximating one half of their natural lives (twenty-four months)

YELLOW ATROPHY OF THE LIVER

ACUTE, SUBACUTE AND HEALED ¹

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Acute yellow atrophy of the liver is a relatively rare malady in its clinically recognizable form, and when it is of a sufficient degree of severity to exhibit its classic clinical picture, it is almost invariably fatal. There are reasons for believing, however, that this disease of obscure etiology may exist in forms which are not of such rarity or fatality as are usually ascribed to it.

For many years pathologists have described cases in which the lesions of the liver indicated a healing or healed stage of acute yellow atrophy, pointing to the probability, if not proving to the satisfaction of all, that recovery from a severe attack of the disease may occur. In 1895, Marchand ¹ clearly recognized the hyperplastic, regenerative nature of large nodules of hepatic cells which are commonly found in such livers, and which in some instances seem sufficient to carry on the function of the organ. In 1909, McDonald and Milne ² described healing stages of the disease, and in 1911, Mallory ³ classified as a distinctive group a "toxic cirrhosis" of the liver consisting of healed lesions of acute yellow atrophy which he was able to recognize by their characteristic histologic changes.

During the years immediately following the World War a remarkable increase in the incidence of acute yellow atrophy was observed in Germany. In 1913, Umber's ⁴ statistics showed no instance of liver atrophy among 84 cases of hepatic disease, in 1920, there were 2 cases of atrophy among 200 similar cases, and in 1921, there were 11 instances of this disease among 149 cases. Seyfarth ⁵ noticed a similar increase at Leipzig. Before 1915, he observed at necropsy 1 case a year on the average, while from 1915 to 1921 he saw 29 cases. Reports from pathologists and clinicians throughout Germany attested to the general increase in the disease.

¹ From the Department of Pathology, Vanderbilt University Medical School

1 Marchand, F. Beitr z Path Anat u z allg Pathol **17** 206, 1895

2 McDonald, S., and Milne, L. S. J Path & Bact **13** 161, 1909

3 Mallory, F. B. Bull Johns Hopkins Hosp **22** 69, 1911

4 Umber, F. Klin Wchnschr 1922, **1** 1585, 1922

5 Seyfarth, C. Deutsche med Wchnschr **47** 1222, 1921

With this increased incidence, an opportunity was afforded to study cases with reference to the possibility of atypical or milder attacks which might be followed by recovery. As a result, several cases of undoubted instances of spontaneous recovery are now on record. Such cases have been recorded by Umber,⁶ Huber and Kausch,⁷ Brutt,⁸ and others, according to Strumpell,⁹ Seyfarth and Brutt, one must now recognize subacute and chronic forms of yellow atrophy.

Recently Pratt and Stengel¹⁰ reported several cases of healed yellow atrophy or "toxic cirrhosis" from their own material and from that of Dr. Mallory's laboratory. They conclude that classic acute yellow atrophy of the liver is simply a severe, rapidly fatal type of a disease, which occurs also in a mild form, it produces few, if any, symptoms during the acute stage, but ends in cirrhosis. The authors emphasize particularly the histologic characteristics of this type of cirrhosis, described by Dr. Mallory as "toxic cirrhosis," which is readily recognizable in its healed state and distinguishable from alcoholic and other types of cirrhosis.

In a series of 130 autopsies performed in the department of pathology at the Vanderbilt medical school during the period of one year (1926), there were 3 cases of yellow atrophy, 1 acute, 1 subacute and 1 healed. These cases seemed worthy of record because of the relatively high incidence of the disease in a short series and because of the possible relation of syphilis as an etiologic factor in two cases, they are reported also in order to emphasize the possibility of recovery from a relatively severe destruction of the liver apparently without symptoms and to describe the histologic characteristics which make it possible to diagnose a healed case of yellow atrophy grossly and microscopically.

CASE 1—History—A colored boy, aged 8, entered the hospital complaining of headaches, inability to walk and blindness. The present illness began about ten months previously with headaches, which had become progressively worse. Four months before admission, his father had noticed that the boy walked on his toes and had a tendency to fall forward. The patient went to bed six weeks prior to his admission and had not been able to get up since that time. He did not have focal symptoms or fever, but he was extremely weak. The headache was worse when the patient sat up. He vomited, but the vomiting was not projectile. Up to the time of the present illness the patient had always been in good health. He did not have a history of syphilis, and the Wassermann reaction was negative. He had lost his vision, and optic atrophy and increased intracranial pressure were present.

Physical Examination—Examination gave evidence of cerebellar tumor, and decompression was performed. Cellulitis of the neck developed, with fever and

6 Umber, F. *Deutsche med. Wchnschr.* **45** 537, 1919.

7 Huber, O., and Kausch, W. *Berl. klin. Wchnschr.* **57** 81, 1920.

8 Brutt, H. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **36** 29, 1923.

9 Strumpell, *Deutsche med. Wchnschr.* **47** 1219, 1921.

10 Pratt, J. H., and Stengel, A. *Tr. A. Am. Phys.* **41** 100, 1926.

rapid pulse The condition grew worse, and the patient died fourteen days after admission

Morbid Anatomy—The condition was diagnosed as acute yellow atrophy of the liver, necrosis of the cerebellum (postoperative) and acute infectious encephalitis The liver weighed 610 Gm, it appeared small Over the convex surface were a few slightly elevated lobules from 3 to 4 cm in diameter, these lobules were brownish, elsewhere the liver was reddish On section, the appearance was mottled

The microscopic appearance was that of typical acute yellow atrophy Apparently the necrosis was recent The skeletons of the lobules remained, the sinuses being distended with red blood cells The liver cells next to the necrotic areas

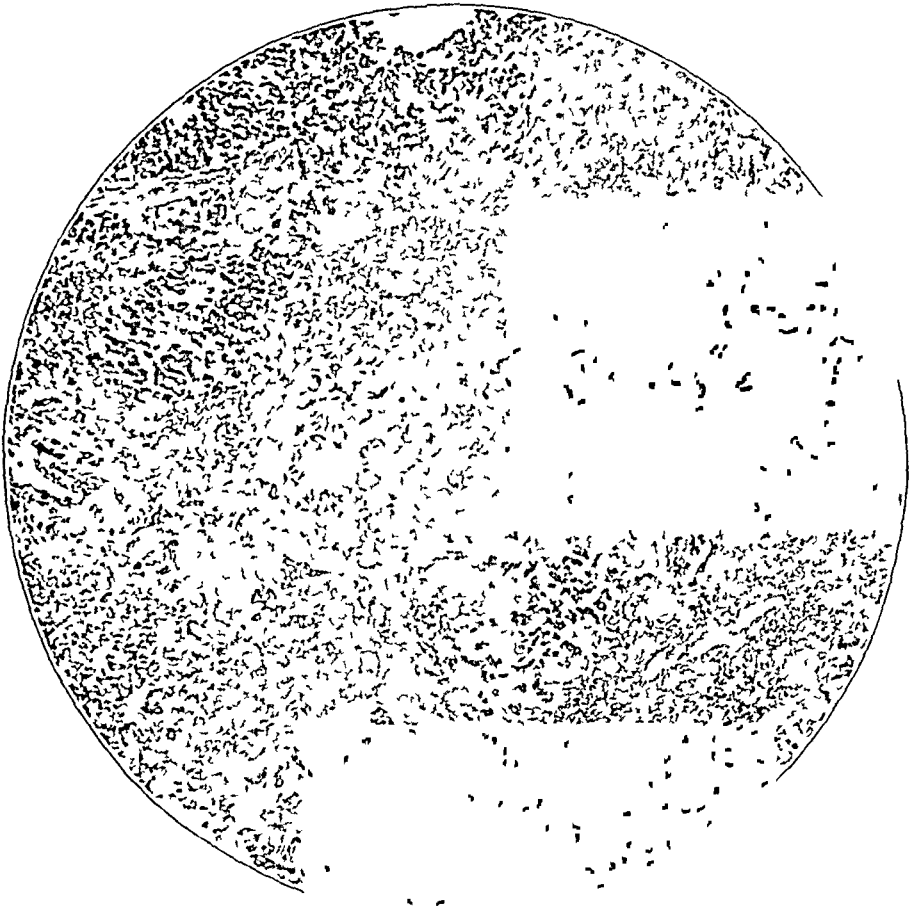


Fig 1—Section of the liver from case 1

were in various stages of degeneration and necrosis Fat vacuolization was especially prominent Bile pigmentation was not observable and there was no regeneration The destruction was more marked in the central portion of the lobules about the hepatic venules than around the portal areas The distribution of the injury was, however, not uniform All liver cells in many lobules were destroyed over extensive areas, and in others the central portion of the lobules was more or less extensively injured with advanced degeneration of all the cells in the remaining portions, adjoining such areas were large blocks of lobules in which all the hepatic cells seemed to be normal The degeneration and necrosis seemed to advance to the lobules contiguous to those already destroyed

In this case all the symptoms were attributed to a tumor of the brain, and the lesions indicated that the injury to the liver had occurred recently Jaundice was not observed, and in microscopic sections there

was no evidence of a biliary obstruction. Most pathologists attribute the jaundice which occurs uniformly in severe cases of several days' duration to an obstruction in the smaller bile ducts due to plugs in their lumina. Such plugs were obvious in case 2, but were absent in this case.

CASE 2—History—A colored woman, aged 26, entered the hospital complaining of weakness, nausea and headaches. The onset of her present illness was three weeks before admission. Weakness was increasing, and she vomited four or five times a day. Two weeks previous to admission, she had given up her work

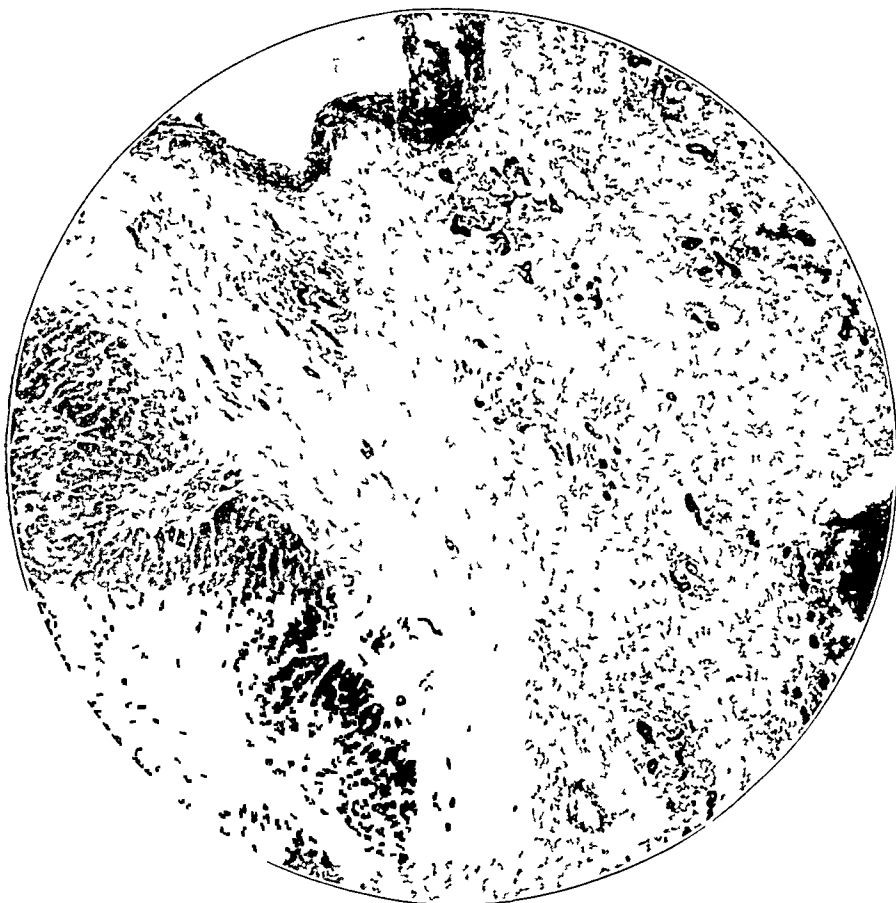


Fig 2—Section of the liver from case 2

and had gone to bed. At that time she had noticed that her eyes were becoming yellow, and they had remained so. She had had three attacks of vertigo, during which she had been completely blind. Until her present illness her health had been good. She had had typhoid fever in early life and influenza and pneumonia in 1920. She was a widow and had had one child, stillborn, and a miscarriage.

Physical Examination—Examination revealed jaundice, she did not have fever. Examination of the blood revealed White blood cells, 6,850, red blood cells, 4,200,000, hemoglobin, 85 per cent, and clotting time three minutes. Bile, albumin and red blood cells were found in the urine. The Wassermann reaction was positive. Eight days after admission, the patient had edema of the legs and some ascites. The face was puffy. There was tenderness in the right side of the abdomen, the liver was not definitely felt. A mass was felt in the epigastrium.

The stools were clay colored. Three weeks after admission, the patient went into coma. Because of tenderness and the mass in the epigastrium, she was transferred to the surgical department. An exploratory laparotomy was performed. The gallbladder was not enlarged. The patient's condition grew worse, and she died twenty-two days after admission.

Morbid Anatomy—Subacute yellow atrophy of the liver, and acute hemorrhagic bronchopneumonia were diagnosed. The liver weighed 570 Gm. The consistency was rather soft, and the organ was flexible. The surface was coarsely and irregularly nodular, the nodules being orange-brown and slightly elevated. The tissue between these structures was dark reddish brown, soft and fibrous. The nodular masses contained much bile pigment and were apparently areas of remaining liver tissue. The soft reddish areas were regions in which the liver cells had been destroyed.

Microscopically, there was typical yellow atrophy with a progression of acute necrosis, phagocytosis and a polymorphonuclear and large mononuclear cell exudate. Evidence of regeneration of the hepatic cells was seen, and much intracellular and extracellular bile pigment. Obstruction to the larger bile passages was not evident although numerous bile-stained plugs were found in the smaller ones.

This case is of particular interest in that, while it is pathologically a typical instance of subacute yellow atrophy, having lasted five weeks, it serves to emphasize the difficulty of distinguishing this disease in its early stages clinically from catarrhal jaundice. It could not be determined during life that the liver had diminished in size. At the time of operation, the margin of the liver was down to the costal margin. Leucine or tyrosine crystals were not found, and the stools were described as completely acholic.

The history of a stillbirth, a miscarriage and a positive Wassermann reaction suggests the possibility of syphilis as an etiologic factor. The number of cases of acute yellow atrophy associated with syphilis is relatively so high that many concede that in certain cases it may play an important rôle (Heixheimer, Stumpcke and Strauss). The association of acute yellow atrophy with syphilis cannot be explained as a result of hepatic injury due to arsenical therapy. A similar association was frequent in cases in which the patient was not so treated, as in the present instance in which intravenous therapy had not been used. It is doubtful that arsphenamine alone would ever produce an acute yellow atrophy in a normal person. Syphilitic infection is perhaps rather to be regarded as one predisposing condition to acute yellow atrophy, which may be precipitated by intravenous injection of arsenicals or by other causes.

CASE 3—History—A white man, aged 26, entered the hospital complaining of difficult and painful urination. He had had typhoid fever and pneumonia at the age of 14. Gonorrhea had been present several years before his admission to the hospital. The present illness began about six months previously.

Physical Examination—Examination showed ulcer of the glans, stricture of the urethra, extravasation of urine, saddle nose, a positive Wassermann reaction and a nodular liver. The patient developed bronchopneumonia, acidosis and acute renal insufficiency, and died on the second day after admission.

Morbid Anatomy—The condition was diagnosed as healed atrophy of the liver, acute urethritis, prostatitis, cystitis, and acute bronchopneumonia

The liver weighed 1,150 Gm. It was tremendously distorted and lobulated, the lobules being irregular and nodular instead of smooth. The consistency was firm. Between the larger lobules were areas in which the parenchyma of the liver appeared to be missing, and in which only connective tissue, bile ducts and blood vessels remained. On section, the lobulated foci consisted of large masses of regenerated liver tissue, while the intermediate softer areas apparently did not contain parenchyma. The whole process seemed to be an old one, not active. There were fibrous adhesions over the dome. Ascites was not present.

Microscopically, in the contracted areas the cells of the liver had completely disappeared, leaving a collapsed, contracted, dense connective tissue stroma containing bile ducts which outlined the skeletons of previous lobules. Throughout this fibrous tissue there were many lymphocytes and plasma cells, and occasionally polymorphonuclear and mononuclear leukocytes. The large areas of hepatic



Fig. 3—Liver from case 3, showing the healed stage of yellow atrophy

parenchyma presented normal appearing liver cells without definite lobulation. There were areas of regenerated liver cells, these were definitely circumscribed by the dense atrophic stroma and did not show any evidence of progressive injury. The process appeared to be a completely healed stage of yellow atrophy.

The gross appearance of the liver in this case left no doubt that there had been an extensive destruction of the hepatic parenchyma, involving large areas of the liver, and that the remaining islands of liver cells had regenerated to form the massive nodules of functional tissue. There was no scarring such as one finds in the syphilitic liver as a result of the healing of gummas. The atrophic portions were not formed of scar tissue but had the appearance of a collapsed stroma which had become indurated, this was confirmed by histologic study. The more or less regular architecture of a previous lobulation remained in the

atrophic areas The persistence of such a lobulation, which indicates that there had been an acute destruction of all the liver cells in areas involving many entire lobules, is the histologic criterion by which Malloiy was enabled to classify certain cirrhotic livers into a group which he calls "toxic cirrhosis," and which he regards as the healed stage of a destructive lesion identical in its beginning with acute yellow atrophy

In case 3 the liver did not bear any similarity to the chronic progressive type of cirrhosis, but in its gross and microscopic features it

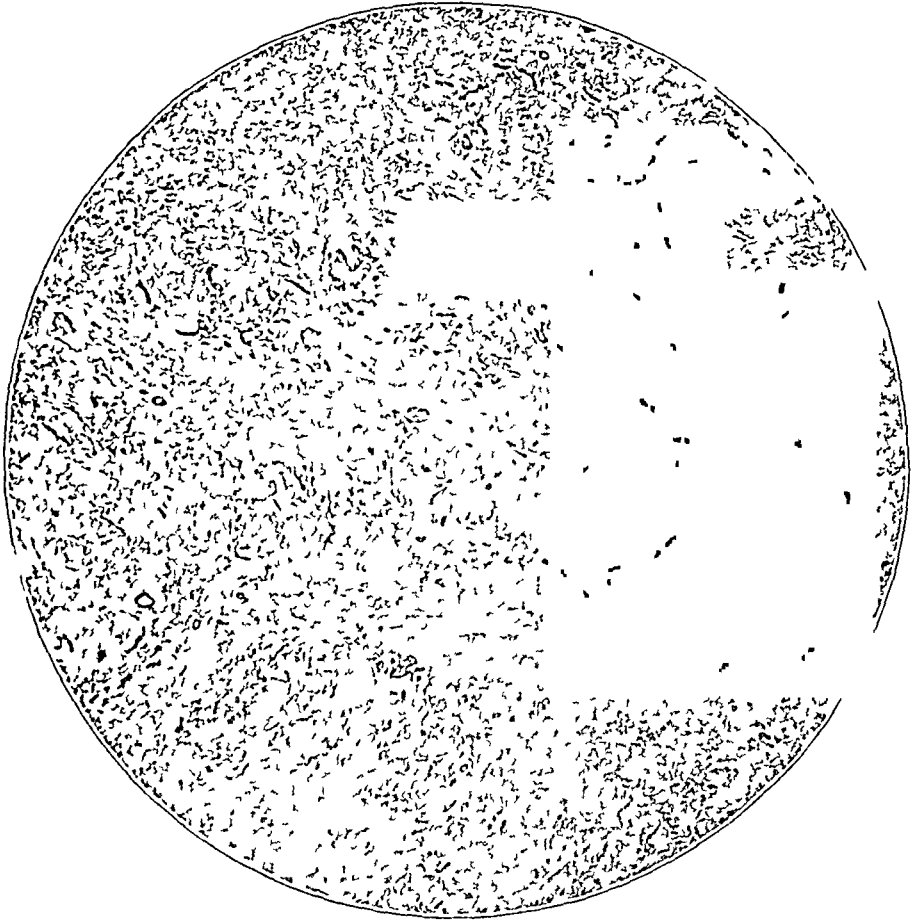


Fig 4—Section through an atrophic area in the liver from case 3 Persistence of lobulation is evident

resembled most of the hitherto described instances of subacute or chronic stages of yellow atrophy in that there were both the extensive areas of atrophy and the large nodules of hyperplasia In this case, however, the lesion was healed

COMMENT

These three cases illustrate the series of events that may result from an acute yellow atrophy, namely, the acute, subacute and the healed stages Intermediate stages between the subacute and the healed have been recorded, these deserve to be called chronic Such are the cases

studied by Marchand (6 months), McDonald and Milne (7 months), and others. In case 2, necrosis was still advancing after the patient had been ill with jaundice for more than four weeks. Though the clinical history referable to damage of the liver was wanting in case 1, microscopically a rapidly degenerative lesion was seen, which may have developed in a few hours or in a few days at most. It would appear from this case that intense bile staining of the hepatic parenchyma, so frequently observed in yellow atrophy of the liver, may be the result of abnormal function and excretion of this pigment by the cells that remain rather than of a biliary obstruction coincident with the injury, for it is absent in the acute stage.

It is to be noted in these three cases that the gross and the microscopic appearance of the liver were characteristic, and did not suggest that acute yellow atrophy is an end-result of an extensive central necrosis like that which may occur following intoxication with such chemical poisons as chloroform or with streptococcic and other infections. The lesions are essentially focal in character, do not affect the hepatic lobules uniformly and are relatively large, consequently, in all stages the morbid anatomy of the liver is that of complete destruction of entire areas of parenchyma with an escape of the larger or smaller areas, which in time become hyperplastic. The process differs in this respect from the effect of known toxic agents circulating in the blood and suggests the presence of some unknown local disturbance in the liver, irregular in its distribution, as an essential or contributing factor. In the subacute, chronic and healed stages, the liver grossly appears coarsely lobular and irregular in the extent of lobulation. If the lesion is healed, it is necessary to determine histologically that entire lobules of hepatic parenchyma have been destroyed in order to make a diagnosis of the condition. As Mallory pointed out, one must find the skeleton of former lobules as outlined by a persistence of bile ducts with a collapsed vascular stroma between.

It does not seem justifiable, however, to diagnose the condition of a healed liver as "toxic cirrhosis," if by that term is meant the end-result of a central necrosis of the type so commonly seen as a terminal event after certain severe infections or after chemical poisoning. Rather, acute yellow atrophy should be considered as a distinct disease with characteristic irregularity in the extent of its lesions, and of unknown etiology, it is not duplicated by any known intoxication. Consequently, we favor the continued use of the terms acute, subacute and chronic stages, as emphasized by Strumpell, Seyfarth and Brutt, and the term a healed stage of yellow atrophy. Although these designations are imperfect, we believe they should be retained in order to preserve the identity of this peculiar disease, pathologically as well as clinically, until it can be given a more precise definition on etiologic grounds.

SUMMARY

1 Cases illustrative of an acute, a subacute and a healed yellow atrophy of the liver are presented

2 Recovery from acute yellow atrophy is probably more frequent than is generally believed

3 Different stages of the disease have been accurately recognized pathologically, namely, acute, subacute, chronic and healed stages

4 In the healed stage the liver is grossly and irregularly lobulated. The hepatic parenchyma is represented by irregular masses of hyperplastic liver cells, which are separated by a vascular, collapsed stroma in which the skeleton of previous lobules persist to a greater or less degree. From this histologic picture the diagnosis may be made.

5 As the initial lesion of acute yellow atrophy differs in distribution and in extent, if not in kind, from that of the ordinary toxic central necrosis, and as we are yet ignorant of the etiology, it is believed that the term "healed yellow atrophy of the liver" is preferable to the term "toxic cirrhosis" as applied to the condition of the liver which is healed.

POLLINOSIS

CONSTITUTIONAL AND LOCAL FACTORS

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The wide prevalence of hay-fever alone would justify presentation of any new concept offering possibilities of increased therapeutic efficiency. Conservative statisticians estimate that fully 1 per cent of the population of the United States is afflicted with hay-fever¹. The malady is sufficiently incapacitating, but when it is considered that 65 per cent of all persons with hay-fever finally become asthmatic,¹ the need for further developments in treatment becomes even more obvious. Interest in these sufferers is not alone humanitarian, for the economic loss to the victim is often great. Those who do not have hay-fever know well the debilitating effect of an ordinary acute coryza, and realize the struggle of those who must work at full efficiency while semiprostrated for weeks or months with an unrelenting rhinitis. Even the welcome asylum of the hay-fever resort, usually located in a heavily timbered area in which weeds were few, has in great measure lost its power to give relief, increasing popularity having resulted in the building of large hotels, the clearing and cultivation of acreage and the consequent proliferation of weeds.

Hay-fever, recognized in the history of medicine for nearly 400 years, since its description in 1565 by Botallus of Pavia, does not fail to justify its name as much as some have asserted. It is true that the major portion of cases in the United States occur some time after the period of timothy pollination and are attributable to the pollination of ragweed, but hay-fever was so designated and studied in England long before the American literature contained extended references, and in England even now the disease appears to be more prevalent in May and June, being well on the wane in early August². Hay-fever and rose-fever, however, are descriptive titles which are too often incorrect both in their etiologic insinuations and in their intimation of a febrile reaction. A truer descriptive title should carry with it either the implication of an allergic state in the patient or a more accurate designation of the provocative cause. Since pollens of one kind or another are almost invariably the immediate agent producing seasonal rhinallergic reactions, we propose to adopt the term "pollinosis". It is true that

¹ Balyeat, R. M. Hay-Fever and Asthma, Philadelphia, F. A. Davis Company, 1926, p. 12.

² Vaughan, Victor C. Epidemiology and Public Health, St. Louis, C. V. Mosby Company, 1922, p. 65.

allergens other than pollens, such as iris root, animal dander or dust, will produce the symptoms of vasomotor rhinitis even with seasonal recurrences, but if the statement that 95 per cent of all such cases are attributable to pollens is correct, the term "pollinosis" will fit the case as satisfactorily as do the designations of the majority of known diseases.

The functional pathology of pollinosis can be satisfactorily discussed only in conjunction with the pathology of allergic reactions in general. Only those pathologic observations that have a direct bearing on certain concepts will be presented in this article. Anaphylactic shock is a constitutional reaction, its site apparently being intracellular. The outstanding recognizable functional alteration consists of increased spasticity of smooth muscle.

General anaphylactic reactions present different clinical pictures in different experimental animals. In the guinea-pig, after a preliminary mild stage in which there is evidence of nasal irritation with sneezing and scratching of the nose, the symptoms become chiefly respiratory, comparable to those observed in a human being with asthma, and at necropsy the outstanding feature is pronounced spasm of the smooth muscles of the bronchioles.

In rabbits that have died from anaphylactic shock, distention of the lungs is not observed, but the evidence points to a pronounced tonic spasm of the muscular coat of the pulmonary arterioles. There may possibly be a similar increased tonicity in the systemic circulation.

In dogs the outstanding feature is a pronounced fall in blood pressure, apparently due to some action on the neuromuscular nerve endings. With this, but not dependent on it, there is an increased flow of lymph and a severe local reaction in the intestines. This amounts practically to an acute enteritis with edema and petechial hemorrhages in the mucous membrane of the gut, the lumen of which is often filled with mucus mixed with blood. Manwaring³ has found that the liver in dogs is a most important organ in the production of anaphylaxis. With the liver out of the circulation, anaphylactic shock does not occur in dogs. Weil⁴ suggests that most of the circulatory disturbance in the dog may be attributed to obstruction in the portal circulation.

He suggests that the differing symptoms in these three types of laboratory animals are due primarily to differences in quantitative distribution of smooth muscle. He finds there is an astonishing development of the bronchial musculature in normal guinea-pigs, while the pulmonary arteries of rabbits present a remarkable degree of muscular development. The walls of the hepatic veins of dogs differ from those of the other animals in showing again a high muscular development. It

³ Manwaring and Crowe. *J. Immunol.* **2**: 517, 1917.

⁴ Weil, Richard, quoted by Zinsser. *Infection and Resistance*, New York, The Macmillan Company, 1923, p. 437.

is true, particularly among dogs and rabbits, that not all animals selected for experiments respond equally well to induced anaphylaxis. It seems possible that this variability may depend, in part at least, on the varied distribution of these muscle preponderances. This suggests attractive speculation as to why some allergic persons develop hay-fever or asthma, others headaches or the symptoms of an acute gastro-enteritis, while others show predominantly dermal manifestations.

That anaphylaxis may be manifested only as a local reaction is demonstrated by the classic experiments of Arthus,⁵ who, while working on rabbits, found that repeated subcutaneous injections eventually gave rise to edema, sterile abscesses and even gangrene at the sites of inoculation.

Coca⁶ maintains that experimental anaphylaxis and clinical allergy, while presenting features of greatest similarity, cannot be considered as strictly identical, because in the latter it has not been definitely proved that there is an antigen-antibody reaction. Van Leeuwen⁷ presents evidence that clinical allergy actually is an antigen-antibody reaction. Kolmer⁸ believes that Coca's insistence on the demonstration, by passive transfer, of antibodies in the serum of a sensitive person is too rigid, since antibodies may be developed in a sensitized animal, including man, without being successfully transferred by injecting the serum into another animal. He doubts the justification for making a division on the basis of the ability to demonstrate antibody production. The technic for discovering antibodies is too imperfect. It is also possible that antibodies may be present in cells when their presence in the blood cannot be demonstrated.

The symptoms of pollinosis result from the contact of a sensitive person with a specific allergen, usually a pollen protein. The reaction may be local, limited to the upper part of the respiratory tract, or it may become generalized, with the symptoms of asthma predominating.

It seems reasonable to suppose that the reaction in the nasal mucosa may be a purely local sensitization reaction, but it must be borne in mind that nearly all of these patients show evidences of a generalized sensitization in the positive cutaneous reaction at a point far removed from the nose. All such cases of pollinosis should be considered systemic and the general or systemic point of view should determine the method of treatment. But is pollinosis purely systemic, or does local sensitization also play a part? If the pollen protein were to gain access to the body

⁵ Arthus. *Compt rend Soc de biol* 48 817, 1903

⁶ Coca. *Tice's Practice of Medicine*, Hagerstown, Md, W F Prior Company, Inc, 1 110, 1920

⁷ Van Leeuwen, W. *Allergic Diseases*, Philadelphia, J B Lippincott Company, 1925

⁸ Kolmer. *Infection, Immunity and Biologic Therapy*, Philadelphia, W B Saunders Company, 1924, p 598

through some other portal, such as the skin, the stomach or the colon, would the symptoms still be those of "hay-fever," indicating that the reaction is entirely general but with predominant symptoms in the nasal mucosa? There is no doubt that nasal symptoms are a part of a generalized reaction. I have already referred to the nasal irritation in anaphylactic guinea-pigs. Patients not infrequently experience sneezing during preseasonal desensitization when the hypodermic dose approaches the limit of tolerance. Bernton has mentioned a most interesting case of a man sensitive to dust, who, shortly after the hypodermic injection of dust extract, the nature of which he did not suspect, complained of an uneasy sensation in the nose, saying that it felt as though he were inhaling dust.

While sneezing clearly appears to be a factor of systemic reaction, there is also evidence that local sensitization plays a part.

I have elaborated my method of treatment on the basis of the following hypotheses. While the treatment is in general orthodox, I present an additional conception on the systemic side which has not received the consideration I believe it deserves.

- 1 Pollinosis is primarily a constitutional disease in which the patient's tissues are generally sensitive to the particular pollen that causes the symptoms. Nasal localization is sometimes a resultant of the systemic reaction. To obtain the best results, the constitutional factor must be taken into consideration.

- 2 The localization of the reaction in the nose may be due in part to a specific sensitization of the tissues of the nasal mucosa.

- 3 The factor deciding nasal localization may equally well be non-specific, such as mechanical irritation in the nose. Such a nonspecific provocative cause usually would not, however, produce the symptoms if a specific constitutional predisposition did not exist at the same time.

- 4 In a person with pollinosis there may be a coexistent sensitization to some protein which would not cause the symptoms of "hay-fever," but the reaction to which, superimposed on the pollen reaction, enhances the manifestations of the latter.

The first postulate scarcely requires further elaboration, it should be granted by all. The second proposition appears equally logical. The Arthus phenomenon mentioned demonstrates experimentally the possibility of a local tissue sensitization reaction. If one can obtain a positive skin test on the back or arm of a person with pollinosis, it is but logical to assume that a similar local sensitization reaction, strictly specific, will occur in the nasal mucosa. The positive ophthalmic reaction is a similar example. Indeed, this conception was the rationale of the preseasonal desensitization with nasal sprays containing increasing concentrations of the specific pollen recommended a few years ago by

McKenzie⁹ This treatment alone, however, does not take into consideration the systemic desensitization I used it through one season, directing the patient to apply the doses several times daily with an atomizer, at the same time, I treated him for the systemic condition by the usual preseasonal hypodermic inoculation The results were good

Cooke, Duke and others have reported cases of typical seasonal pollinosis in which the results of the sensitization tests with pollens were negative I record three such cases Among 200 cases, Kern¹⁰ reports 4 typical seasonal cases in which the patients gave negative skin reactions to pollens Two of these received conjunctival tests, one being weakly positive thereto Three were treated with pollen extracts appropriate to the season, with good results He believes that these are true cases of pollinosis with local sensitization only It would have been of interest to know whether nasal instillations of pollen extract would have produced a reaction, also whether the skin tests did or did not become positive after subcutaneous desensitization

On the other hand, the recent work of Bernton,¹¹ in which he shows that one may be sensitive to only one of the constituent proteins of the pollen, may account for these negative reactions He found that just as one may give a negative reaction to the whole wheat protein and a positive reaction to one of the constituent wheat proteins, so one may give a negative reaction to the usual pollen protein, but a strongly positive response to one of its fractionations

The third postulate—that nonspecific irritation increases the local symptoms—in my opinion, accounts for the benefit often attributed to and actually following nonspecific therapy Whoever has seen a spiculated pollen spore under the microscope requires little imagination to understand that the pollen itself, besides its specific antigenic properties, is an actual mechanical irritant of decided significance Auer¹² has convincingly shown experimentally how a mechanical irritant will determine localization of the reaction in a sensitized animal or person Xylol applied to the ears of nonsensitized rabbits did not produce a great degree of inflammation On the other hand, when xylol was applied to sensitized animals which were then given otherwise ineffective doses of antigen local necrosis occurred He concluded that the inflammatory action of xylol caused accumulation of effective amounts of antigen in the locality affected

The following illustrative cases will bring out some of these points more clearly and will preface a more extended discussion of the fourth postulate

9 MacKenzie G M Desensitization of Hay-Fever Patients by Specific Local Applications, *J A M A* **68** 787 (March 18) 1922

10 Kern Ann Clin Med **5** 371, 1926

11 Bernton Harry S South, *M J* **20** 257 (April) 1927

12 Auer Proc Soc Exper Biol & Med **17** 93, 1919

ILLUSTRATIVE CASES

CASE 1—The patient had had fall hay-fever for several years, which came on any time between the 1st and the 15th of August. She had been given courses of ragweed desensitization, never with satisfactory results. On being tested, she gave a negative reaction to ragweed, a three plus reaction to sunflowers and two plus reaction to golden rod. Following daily hypodermic desensitization with golden rod for three weeks prior to August 1, the patient experienced practically 100 per cent relief throughout the 1926 season.

Antecedent failure was due to the physician's failure to realize that sensitization is specific and may be due to some pollen other than ragweed. If a careful history had been taken, this would have been suspected, since ragweed pollinosis never begins before the 15th and rarely before the 20th of August.

CASE 2—The patient had early spring and fall hay-fever and was strongly sensitive to roses, orchard grass, June grass and sunflowers and mildly sensitive to daisies and ragweed. There was a negative reaction to timothy. Some manufacturers of pollen extract advise that since 90 per cent of spring and summer pollinosis is due to timothy and 90 per cent of the fall variety to ragweed, these two pollens may be used with the expectation of 90 per cent of relief.

This is one of the many examples of the cases in which desensitization with timothy would have been a complete failure.

CASE 3—A woman who had vasomotor rhinitis of four weeks' duration reacted clearly to the pollen, but not to the grain, of corn. At first she denied eating corn, but later recalled that she had been eating hominy daily during the period of sneezing and not previously. She lived in the city, and the possibility of local pollen effect seemed remote. She omitted corn and hominy from the diet, and was promptly relieved. I have had two patients who were sensitive to the pollen but not to the protein of corn, and who developed attacks of sneezing after eating food containing corn. In these cases there was a reaction due to a constitutional sensitization, the portal of entry was the stomach, but the constitutional reaction was manifested in the nose.

This is an example of pollinosis in which the local symptoms are not due to local reaction. The observation that the sensitization was due to an article which customarily causes nasal symptoms on local contact is of interest.

While probably most cases of perennial vasomotor rhinitis accompanied by sneezing in and out of season are dependent on local contact, as with powders or soaps containing onion root, horse dandel, the dust from feathers and rabbit hair, house dust, etc., I have had a series in which the sneezing followed the ingestion of food to which the patient was sensitive. This is not infrequent in the experience of others, but differs from the last two cases described in that these patients were sensitive by test to the pollen but not to the food, and yet had symptoms on contact with the latter.

CASE 4—The patient with severe rhinorrhea occurring during the ragweed season, who was found strongly sensitive to the hair of dogs and rabbits, less so to feathers, dahlias, orchard grass and dandelions, and with negative reactions to foods, did not improve on avoidance of these causes or on local palliative treatment of the nose. Roentgen-ray examination, however, showed evidence of a maxillary sinusitis, and drainage of the sinus gave prompt relief.

Here sensitization may not have played a part, but the symptoms were those of pollinosis, and headache, local pain or tenderness, fever or leuko-

cytosis were not present, as one would expect in sinusitis. A local mechanical factor produced allergic symptoms in a person shown by positive skin tests to be in an allergic state.

CASE 5—The patient, whose only symptom was sneezing, did not give any positive food, pollen or epidermal reactions, and his symptom was promptly relieved by the extraction of an abscessed upper canine tooth.

This case and case 4 show that while attention is being directed to allergy, the possibility of a purely local pathologic change must not be overlooked. I have no doubt that those cases of asthma in which the rhinologists give relief by argyrol tamponage of the ethmoids are associated with local infection.

While the allergist probably fails too frequently to recognize such local pathologic changes, his error has not the same serious significance as that of the rhinologist who submits the patient to unnecessary intranasal operation while the cause is constitutional. A patient with a typical vasomotor rhinitis of eight years' duration had had the polyps removed, the ethmoids operated on, and submucous resection, all without benefit and was then promptly relieved after he avoided the use of orris root, beans, peas, garlic, sweet potato and wheat.

CASE 6—The patient gave mild reactions to the proteins of chicken and of chicken feathers. By avoiding these irritating proteins, he was relieved of a mild condition of asthma, which consisted chiefly of tightness in the chest without outspoken attacks. Although not sensitive to ragweed or other pollens, and although not manifesting the symptoms of pollinosis, he is ill at ease during the pollen season, more so when in the country than in the city and particularly when in the neighborhood of ragweed.

In this case it seems reasonable to conclude that the purely mechanical irritation from pollen in an otherwise mildly allergic person produces the symptoms.

CASE 7—The patient had a typical ragweed hay-fever of five years' duration and a history of attacks of urticaria of fifteen years' duration. Attempts at ragweed desensitization during the preceding four years had been unsuccessful. The patient was first seen during the hay-fever season, she was suffering with severe hay-fever which had not been mitigated by preseasonal desensitization. She was clearly sensitive to daisies, sunflowers, roses and ragweed. She was tested with various foods and reacted to the proteins of egg, wheat, carrot and pepper. After omission of these foods from the diet, the hay-fever was promptly relieved.

I shall now discuss the fourth postulate. I have recorded elsewhere¹³ my theory of an allergic equilibrium or balanced allergic state. Briefly, the hypothesis is as follows. A person may be sensitive to some food protein, such as a food with which he comes in frequent, even daily, contact, and yet remain free from symptoms. Peshkin and Rost¹⁴ and Rackemann¹⁵ have found that about 10 per cent of children without symptoms of allergy are sensitive to one protein or another. They are

13 Vaughan, W. T. South M. J. **27** 749, 1924, Virginia M. Monthly **51** 472, 1924.

14 Peshkin, M. M., and Rost, W. L. Incidence of Protein Sensitization in Normal Child, Am. J. Dis. Child. **23** 51 (Jan.) 1922.

15 Rackemann. Am. J. M. Sc. **163** 87, 1922.

allergic but are in equilibrium. The tissues are able to handle a given quantum of the allergen without upsetting the allergic balance. Perhaps desensitization from frequent ingestion of small amounts is a factor. An overdose of the allergen, however, will upset the equilibrium with consequent precipitation of symptoms.

One may be sensitive to two proteins, maintaining allergic balance while the contact is with one only, but developing symptoms on exposure to both. It may be unnecessary to remove both for relief, the equilibrium being reestablished on the avoidance of one. In the case just described, the patient was sensitive to certain foods, the strongest reaction being to egg. She had eaten wheat and eggs practically daily in the past with no symptoms other than an occasional urticaria. She was allergic but practically in allergic equilibrium. When exposed to ragweed pollen, she developed the typical symptoms of pollinosis. Desensitization gave little or no relief, but another therapeutic procedure remained possible. The food proteins were eliminated, the additional tax on the system was relieved, and the patient returned to a balanced allergic state in spite of continued contact with ragweed proteins.

CASE 8—The patient had suffered from ragweed pollinosis for years. There was an accompanying ragweed asthma, but no asthma at other times during the year. He was strongly sensitive to ragweed and mildly so to the hair of rabbits and dogs, chicken feathers and nine food proteins. He was relieved from hay-fever, but not from asthma, by coseasonal desensitization. There was prompt relief after avoidance of the food and other proteins to which he was sensitive. Through the year he had been able to sleep on feather pillows and felt mattress and to eat the food to which he was sensitive without disturbance of the allergic equilibrium.

My co-workers and I have had several other patients with pollinosis who were not relieved or who were only partially relieved by pollen desensitization, and who have subsequently been further relieved or cured for the season by avoidance of other proteins, usually in the food. Therefore, when a patient with pollinosis does not respond satisfactorily to treatment, he is tested as a matter of routine, with the food and epidermal proteins.

In these cases both factors at work are specifically allergenic. It is my belief that one of the factors may be nonspecific. A person sensitive to a protein but remaining in allergic equilibrium may manifest symptoms after the action of some mechanical provocative cause. This is more often seen in allergic states other than pollinosis. The experimental work of Auer mentioned in the foregoing might be cited as an example. Dermatographia produced after mechanical irritation in an allergic person is an example. A person sensitive to a food which he is eating daily may remain in balance until the mechanical irritation of a tight collar produces a local eczema.

CASE 9—The patient complained of a seasonal hay-fever which lasted from March until the first frost. She gave negative reactions to all of the available pollen proteins. In order to be certain, these tests were all repeated, and the results again were negative. She gave borderline reactions to several foods, and after eliminating them from the diet, she experienced from 50 to 75 per cent improvement. She was not given local nasal treatment while on the diet.

In this case the allergic balance was evidently overthrown by the mechanical irritation of the pollens in the inspired air. This case recalls those described by Kern. It would have been of interest to know whether his negative pollen reactors were sensitive to other proteins, such as food proteins.

CASE 10—The results in this case may be explained in the same manner. A woman had perennial vasomotor rhinitis which however, was decidedly worse during the ragweed season. There was a negative reaction to all pollens, a three plus reaction to the feathers of geese and ducks and to the hair of rabbits, a two plus reaction to oats and rice, and a one plus reaction to lettuce, squash and the hair of dogs. Treatment consisted of avoidance of the irritants. Prompt relief was experienced, and the patient has since gone through two ragweed seasons without symptoms.

COMMENT

I have attempted to show that there are often two, three or even more causative factors or agents which must be taken into consideration in the treatment of patients who have simple pollinosis. The disease is constitutional with local manifestations. Often two factors may be grouped, one as predisposing and the other as exciting or provocative. Usually the predisposing factor is specific, as exemplified in my discussion of allergic equilibrium or the balanced allergic state. The provocative cause may be specific, allergenic, or nonspecific, nonallergenic. The exciting cause may exert its action either constitutionally or locally. Constipation, focal infection, endocrine disturbance, exhaustion, possibly calcium deficiency and the like may play nonspecific parts. For the greatest success, however, the basis of treatment must be a conception that pollinosis is a constitutional allergic disease.

There are other details in a consideration of the treatment, but space does not permit discussion of them. One of particular interest is nonspecific desensitization, as with peptone. Suffice it to say that I have had more poor results than good ones with peptone, but sufficient good results to justify trial when other methods have failed. I do not know precisely how nonspecific desensitization reduces tissue reactivity. Wells speaks of tissue inactivation when, through exhaustion, drug action or other injury, the sensitized cells cannot respond to the antigen-antibody reaction.

The remarkable fact is that early in the development of the present system of pollen desensitization such good results were usually obtained. Short lived saline extracts have now been replaced by more permanently potent glycerin and alcohol extracts. Formerly coseasonal treatment was avoided as dangerous. Since good results from daily coseasonal injec-

tions were first reported in 1923,¹⁶ this method has been generally adopted in appropriate cases. Indeed, Duke¹⁷ has recommended daily inoculations over a shorter time in his preseasonal work, and I am able to say that in the 1926 season I obtained far superior results with the Duke method than with any other preseasonal system that I have employed.

Phillips¹⁸ reports good success with daily coseasonal inoculations. He appears to have obtained excellent results from daily intradermal injections, a method which would appear to have decided advantages and few disadvantages.

The investigations of Bernton already referred to represent another advance in the work with the pollen protein itself and, like the improvements just mentioned, will promote greater success in specific pollen desensitization.

In spite of these forward steps, however, cases remain in which the patients do not respond satisfactorily. In these the application of the concepts brought forward in this paper will further increase the percentage of good results.

A closer liaison between the allergist and the rhinologist is desirable. Local pathologic change serves as a nonspecific predisposing factor and helps to disturb allergic equilibrium. The rhinologist should cooperate to remedy these defects, but he should complete his work out of season. Aside from making sedative applications, he cannot do any good during the attack, and reconstruction work will be productive of harm. It is better to remove polyps, but this should be attended to before the symptoms commence. The patient with pollinosis should consult a rhinologist preseasonally for local renovation at the same time that he consults an allergist for preseasonal desensitization.

Success in the treatment of this disease depends on many factors. Among the more important are the following:

- 1 Recognition of the specific cause
- 2 Ample specific therapy with a proved potent antigen, either preseasonally, or coseasonally, or both
- 3 Prevalence of pollen. Too great a dose of antigen will overcome the the most efficient preliminary desensitization. Conversely, the good results attributed to specific therapy are sometimes due in part to a low prevalence of pollen. Two workers in different sections using identical therapy may observe radically different results due, not to the method, but to differing prevalence of pollen.
- 4 Weather conditions. Sun, wind and rain determine the abundance of seasonal vegetation and the distance to which the pollen will be carried.

16 Vaughan, W. T. Specific Treatment of Hay-Fever During the Attack, *J. A. M. A.* **80** 245 (Jan 27) 1923.

17 Duke. Asthma, Hay Fever, Urticaria and Allied Manifestations of Allergy, St. Louis, C. V. Mosby Company, 1925.

18 Phillips. Relief of Hay-Fever by Intradermal Injections of Pollen Extract, *J. A. M. A.* **86** 182 (Jan 16) 1926.

5 The absence of too great physical alterations in the upper part of the respiratory tract

6 Avoidance of mechanical irritation such as from dust

7 Recognition and removal of other constitutional factors, either allergenic or nonallergenic, which through their presence diminish functional efficiency and help disturb the allergic balance or equilibrium

8 Cooperation of the patient Treatment properly applied is not altogether pleasant It is time-consuming and exacting Other considerations being equal, the more cooperative the patient, the greater will be the anticipation of good results

CORRECTION

In the article by Dr Albert H Rowe, entitled "House Dust in the Etiology of Bronchial Asthma and of Hay-Fever" (*ARCH INT MED* **39** 498 [April] 1927), an error occurred in the last paragraph on page 501 5 per cent salt solution was used, instead of 0.5 per cent solution, as there stated

Book Reviews

SYPHILIS UND INNERE MEDIZIN VON HERMANN SCHLESINGER II Teil Die Syphilis der Baueingeweide Price, 19 50 marks Pp 289 Berlin Julius Springer

The author says in his preface that this work deals with diseases that for the most part are well known, even though there is still lively discussion concerning many of them. He also says that he approaches the subject as a clinician, as an "alter Krankenhausarzt". His aim is to present facts rather than theories. He admits that he is of a skeptical turn of mind and does not accept uncritically all that has been written about visceral syphilis. One sees that he has a knowledge of chemical and other laboratory aids to the diagnosis and understanding of this topic, but it is also clear that in the study of a case Schlesinger does not depend entirely on the van den Bergh test, or the Wassermann reaction, the sedimentation of the blood or on the roentgen ray. There is old fashioned reliance on the history, subjective symptoms, palpation and percussion. It is refreshing to read how syphilis of the liver is diagnosed largely by such symptoms as pain, fever, the size and shape of the organ and by the therapeutic test. Without disregarding the examination of the blood, he tells us how misleading the Wassermann test may be. Some have contended that in this disease there are characteristic numerical changes in the leukocytes. Schlesinger has frequently seen a relative lymphocytosis, but he concludes that "in syphilis of the liver no definite blood formula exists and—with the exception of the serologic examination—the blood findings have no definite diagnostic or prognostic significance." There are scores of helpful diagnostic hints such as only an experienced observant practitioner could give. Thus he says that bloody stools should not lead one too readily to believe that there are esophageal varices or ulcerative processes due to the disease. They may often be due to a mercurial enteritis, the result of over-vigorous medication.

And so all through the subjects of syphilis of the liver, stomach, spleen, kidney, pancreas and bowel, the practical, well tried, clinical features are stressed rather than the newer and theoretical. It is not to be concluded, however, that theory and pathogenesis are overlooked. These are given fair consideration. As a good example may be cited his argument and conclusions concerning arsphenamine icterus. Syphilis and nutritional disturbances furnish the groundwork for the icterus. The drug, however, damages the liver parenchyma and leads to the icterus and liver atrophy, (p 80).

The book is easily read. There is a good bibliography, especially of German literature. To one who wishes help in practical clinical work in syphilis of the abdominal organs, the book may be warmly recommended.

THE CONQUEST OF DISEASE By THOMAS B. RICE, M.D., Assistant Professor of Sanitary Science, Indiana University School of Medicine. Cloth Price, \$4 Pp 363, illustrated. New York The Macmillan Company, 1927.

This interesting book was written primarily for the laity and general students, with three main purposes in view: (1) to set forth the most recent scientific information concerning the transmissible diseases to the end that these diseases may be controlled or perhaps ultimately eradicated, (2) to make the subject interesting, if possible, to the general reader, and (3) to

emphasize the great advances that have been made through scientific methods by comparing the past with the present

One is impressed with the accuracy and fairness of the contents, as well as with their clarity and simplicity, there is little opportunity for disagreement, and the use of highly technical terms is avoided. Much interest is added by short historical accounts of each disease and by a review of many of the superstitions which arose from ignorance, misunderstanding and religious fanaticism

Part one consists of a general survey. Part two is devoted to a detailed study of each disease, grouped according to the manner of transmission. The final chapters are devoted to a consideration of the means of control and explain the rationale of public health administration, sanitation, quarantine regulations, vital statistics, and registration of births and deaths. There are no misstatements of fact, and the author's sincerity and humanitarianism should make a strong appeal to every intelligent reader. Information of this character, presented in such masterly fashion, cannot fail to advance the cause of scientific medicine

TRAITE DE PHYSIOLOGIC, NORMALE ET PATHOLOGENIQUE. Published under the editorship of Drs G. H. Roger and L. Binet, Professors of Physiology in the Faculty of Medicine, University of Paris. Volume 7. Blood, Lymph and Immunity. Price, 65 francs. Pp 502, with illustrations. Paris: Mason et Cie, 1926.

This volume on normal and pathologic physiology deals with blood, lymph and immunity. It is a composite effort of eleven authors, with chapters on the morphology of the blood, hemoglobin and its derivatives, respiratory albuminoids of invertebrates, blood plates, bone marrow, blood coagulation, hemorrhage, blood transfusion, the lacunar system (including edema, dehydration, etc.), lymph and lymph products, lymph glands, immunity (this chapter by Bordet) and anaphylaxis. Each chapter has limited references to the literature. The book as a whole is weakened by the absence of an index at the end, so that one has to hunt for the matter through the schematic table of chapters. The chapter by Bordet on immunity is particularly excellent. It seems strange, however, that in such an ambitious monograph on the physiology and pathology of blood and lymph with chapters on hemorrhage and edema, there should not be a chapter on the various types of anemia. One is also struck by the fact that in the chapter on the physiology and pathology of the blood plates, reference is not made to the recent work of Howell on the significance of the blood plates in hemophilia. The book as a whole, however, is readable, lucid, reasonably comprehensive and up to date.

PROBLEMS OF DISEASES OF THE JOINTS [†]

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When one considers diseases of the joints, two pictures arise before one's eyes

One is that of a boy aged about 20, immovable in bed because of severe pain in his swollen joints, high temperature and palpitation of the heart. After some days or several weeks, the pain and swelling of the joints will disappear perfectly and he will recover, but a mitral incompetence remains and he will be a lifelong invalid. Several years later, a second or third attack of rheumatic fever appears, and perhaps at last a recurrent endocarditis brings on death with the symptoms of a septic disease.

The second picture is that of a woman in an almshouse. For many years, she has suffered from pain in the fingers, wrists, knees and other joints. Most of the joints become more and more stiff and manifest deformities of all kinds. The whole day long she sits in an armchair or lies in bed. She is unable to move her deformed hands, to take a spoon or glass to her mouth, to bring a handkerchief to her nose or to brush a fly away from her face. She is completely dependent on the good will of her nurse, she is forgotten by her family and friends. Month after month passes in the same solitude, though she is contented as long as her pains do not grow excessive. It is interesting to study the mental attitude in these chronic diseases.

One might think that both these forms were different stages of the same disease, the acute and the chronic form, but an exact study, especially of the pathologic anatomic lesions, shows that these diseases of the joints are of a different character.

SYMPTOMS AND SIGNS

The student of pathologic changes of diseases of the joints will do best when he follows the steps of the great masters, and this is necessary for all those who are not pathfinders themselves. In the early dawn of exact pathologic study, Virchow and Volkmann taught

[†] Address given at the formal opening of the Medical School of the University of Rochester, Oct 25, 1926

students to distinguish those diseases of the joints which are of inflammatory character and those in which only the degenerative processes in the joints prevail

The classic signs of inflammation are found in the acute diseases of the joints. The old Roman, Celsus, characterized inflammation as a syndrome consisting of the following symptoms: rubor, calor, tumor, dolor and functio læsa. The inflamed joint is hot and red from the increased flow of blood, it is swollen through exudation into the cavity of the joint and its surrounding tissues, the joint fluid is rich in protein and leukocytes, and the joint is extremely painful and therefore resists attempts on the patient's part to move the affected limb.

In the degenerative form, only slight pain is present, there is no exudation but, instead, a slow degeneration of the cartilage takes place, accompanied by a proliferative outgrowth of osseous tissue.

In accepting this distinction between inflammatory and degenerative proliferative processes, it must be realized that only the acute forms of inflammation present a purely exudative character and that in nearly all cases of inflammation some signs of regeneration are present.

Following the destruction of the tissue in a severe inflammatory process of the joint, repair takes place through the proliferation of connective tissue cells. This process often results in a thickening and retraction of the capsule and in hypertrophy of the synovial membrane. Often ankylosis or adhesions take place between contiguous surfaces and in some instances large masses of new bone are produced.

In the acute arthritis of rheumatic fever, the signs of inflammation are especially pronounced in the synovial membrane. In healthy joints, the latter is a smooth, undifferentiated layer, poor in cells and in blood vessels, which never come to the surface, but which are rich in nerve fibers. In cases of acute rheumatic arthritis, redness and edema of the synovial membrane extending into the periauticular connective tissue are demonstrable at biopsy. The synovitis is characterized particularly by a perivascular and perineural infiltration of leukocytes and mononuclear cells. Homer Swift believes that the intensive articular pain in rheumatic fever is due to the pressure of the inflammatory exudate on the nerves. The cartilages are completely free from blood vessels and nerve fibers, and therefore cannot play an active part in the inflammation or the pain.

Roentgen-ray studies have shown that in all cases of inflammatory disease of the joints the bony framework of the epiphysis is sooner or later greatly diminished and the epiphyseal ends of the bones suggest a cavity. This atrophy of the epiphyseal regions is characteristic of all acute and subacute diseases of the joints and affords a characteristic distinction between the inflammatory and the productive hypertro-

phic processes The origin of this atrophy is not yet perfectly understood It may be that it is due mainly to the inactivity of the painstricken joint Indeed, the maintenance of the normal shape of the cartilages and other joint structures is dependent on activity and pressure As soon as a joint becomes immobile, some degeneration of the cartilages takes place and the osseous matter of the bones decreases However, in some cases that I have seen a protracted immobilization of a normal joint resulted in only slight atrophy of the bones but produced a severe retraction and fixation of the capsule In the atrophy caused by inactivity, the spaces of the bone marrow between the atrophic trabeculae are filled with fat as in normal bones But in the cases of acute inflammations of the joints I have found great infiltrations of lymphocytes and polymorphonuclear leukocytes filling the bone marrow spaces adjoining the affected joint This cellular proliferation produces a dense border surrounding the bony trabeculae Often a zone of osteoid tissue is found at the periphery of this inflammatory process It may be assumed that the rarefied areas seen in roentgenograms of the epiphyseal ends of the bone are the end-results of the thinning and resorption of the trabeculae incident to the inflammatory reaction I have reason to believe that the infectious process does not begin in the synovial membrane but in the bone marrow of the epiphysis, which is recognized as rich in blood vessels The infection may have its origin in the bone marrow of the epiphysis and may extend from that point to the periosteum and synovial membrane, as is the rule in osteomyelitis and tuberculosis of the joints

Dr Kyes of Chicago agrees with this point of view and from his experiments with animals concludes that in general bacteremias the micro-organisms localize especially in the spleen and in the epiphyses of the bones, because in those regions the rate of the blood stream is slow A Fraenkel and his co-workers in Hamburg have often isolated micro-organisms from the bone marrow of the vertebrae and the bone marrow of other regions in a large proportion of the cases of sepsis that they studied Furthermore, Wassermann believed that the production of antibodies takes place especially in the epiphyseal osseous spaces

The inflammatory process which has progressed from the epiphysis to the periosteum now extends to the synovial membrane, and the exudation into the cavity of the joint takes place in most cases This exudate is in most cases free from bacteria, but despite this fact, one should not conclude that the inflammation is not of an infectious character In erysipelas and in many cases of pleurisy, the exudate is also free from bacteria, but it is well established that the bacteria lie in the inflamed membranes However, in gonococcal arthritis, the joint exudate is often rich in gonococci

ARTHRITIS

The word rheumatism is derived from the Greek word rheo, to flow, or rheuma, flowing. This expression implies that a noxious substance flows through the body and acts in many distant regions. This flowing can take place only through the blood or lymph channels.

The term rheumatism has been applied to a great many pathologic conditions, myalgias, neuralgias and arthralgias. I propose here to limit my discussion to a general pathologic anatomic study of the true inflammatory and degenerative-proliferative diseases of the joints.

Secondary arthritis is frequently seen in the course of many infectious diseases such as scarlet fever, dysentery, gonorrhea, cerebrospinal meningitis, puerperal fever and Malta fever. Gerhardt grouped those arthritides of obvious metastatic character under the term, "Rheumatoide Erkrankungen," and he emphasized particularly the tendency toward secondary arthritis in cases of putrid bronchiectasis.

An obstinate type of polyarthritis is sometimes associated with bacillary dysentery. It is still a debatable question as to whether the inflammation of the joints found in this disease is caused by the toxin of the bacillus of Shiga-Kiuse or by a secondary infection with streptococci which have been found in the affected joints.

A painful arthritis is frequently seen in the course of scarlet fever. Since the swelling and tenderness in the joints first manifest themselves on about the tenth day of the disease and begin to decrease in intensity in a few days, the picture is not unlike that found in the serum sickness occurring in the first week following the intravenous administration of large quantities of foreign serum in the treatment of diphtheria, tetanus, or pneumonia type I. True serum sickness is characterized by the presence of fever, urticaria, transient leukopenia followed by leukocytosis, eosinophilia, and by an arthritis of varying intensity. It is tempting to conjecture that the arthritis seen in rheumatic fever is an allergic phenomenon paralleling that seen in serum sickness. In this connection, it is of interest that Boots and Swift have demonstrated that the joint exudate in rheumatic fever is microscopically indistinguishable from that occurring in serum sickness.

Besides the mild arthritis of scarlet fever already described, there is a severe type which comes on in the later stages of the disease. This has been shown to be due to streptococcus metastases.

One of the clearest examples of inflammation of the joints is seen in gonorrheal arthritis. It occurs nearly always in conjunction with an acute gonorrheal infection. Relapses of the arthritis are rare, but they sometimes occur as the sequelae of a new infection with the gonococcus or an acute resumption of activity on the part of a previously quiescent gonococcal focus. There is abundant evidence that the latter process

takes place frequently. It is particularly apt to occur during the puerperium or following excesses in Baccho et Venere, without reinfection, however. I am acquainted with a physician who suffered three severe relapses of gonorrheal rheumatism lasting many weeks. During the arthritis, a tenosinovitis of both hands ensued, which resulted in a bilateral shortening of the fascia palmaris. When the inflammation had ceased, both hands presented the picture of severe Dupuytren's contracture, which greatly hindered the physician in his practice. Painful gonococcal inflammation also occurs in the achilles tendon, and for the most part achillodynia is due to gout or to the gonococcus.

Typical gonorrheal arthritis begins with a high temperature and with inflammation in many joints, but in a short time the majority of the inflamed joints appear to have undergone healing. The process then becomes localized in the knee joint, the ankle joint, or in many of the small joints of the hands, producing almost unbearable pain and disability over a long period of weeks. Roentgenograms of the involved joints begin to show significant foci of rarefaction in the epiphyseal portion of the bones at the end of the second week of the disease. One cannot differentiate these roentgenograms from those seen in acute rheumatic polyarthritis.

In some cases of gonorrheal arthritis, an endocarditis and sometimes a myocarditis occurs. There can be no doubt that this is a symptom of a definite bacterial metastasis, since Leyden and others have isolated the gonococcus in pure culture from the valvular vegetations in endocarditis and from purulent exudate in the joints.

A distressing ankylosis often remains as a sequel to the gonococcal inflammation of the joints. This must be combated early in the disease by a regimen of persistent active and passive motion. Although the impairment of motion of the joints may be due to a simple thickening of the capsule, the usual picture in the late stages of gonorrheal arthritis is that of fibrous adhesions and osseous ankylosis between the adjoining joint structures. A destruction of the cartilages goes hand in hand with this process.

Degeneration and destruction of cartilages of the joints are sometimes seen in other types of severe infectious arthritis. I remember particularly one case of multiple involvement of the joints of the upper and lower extremities which was due to *B. coli* acting its frequent rôle of a secondary invader to a gonococcal infection of the prostate and seminal vesicles. Following the ascending infection of the urinary tract, the subacute polyarthritis ensued and thereafter the patient died.

In Malta fever, polyarthritis is a frequent and characteristic symptom. In this disease the involvement of the joints runs a benign,

though chronic, course The pneumococcus, meningococcus and staphylococcus are occasionally the causes of severe inflammation of the joints, but the commonest organism that is found in the acute polyarthritis is the streptococcus

Singer of Vienna believes that the streptococci form one homogenous group, but, through the work of Schottmuller of Hamburg and Brown, working at the Rockefeller Institute in New York, it has been proved that there are varieties of the micro-organism Schottmuller has described four types of streptococci

1 *Streptococcus non-hemolyticus*, which grows in short chains, does not hemolyze blood on the blood agar plate and appears frequently as a saprophyte in the nasopharynx According to some investigators, it is often found in the joint exudate, blood and pericardial exudate of patients with rheumatic fever

2 *Streptococcus hemolyticus*, which grows in long chains, hemolyzes the blood on blood agar plates and is usually of a higher virulence than 1

3 *Streptococcus viridans*, which grows in short chains On blood agar plates, instead of producing hemolysis, it becomes surrounded by a greenish zone of variable diameter

4 *Streptococcus putrificans*, which is a small coccus that is difficult to cultivate under ordinary laboratory conditions With appropriate anaerobic environment, growth takes place with the production of an ill-smelling odor

The latter organism is sometimes found in the sepsis following abortion, and Rosenow believes that it is this coccus, so often found in the apexes of infected teeth, which is the etiologic factor in some of the arthritides In Rosenow's laboratory, I have seen metastatic arthritides follow the intravenous injection of such anaerobic streptococci into dogs

Streptococcus viridans is found frequently in the crypts of inflamed tonsils and also at the apexes of infected teeth In comparison with the hemolyticus, it possesses a slight degree of virulence It is astonishing, however, that the supposedly mildly virulent viridans, which is apparently a frequent inhabitant of the human pharynx, can so easily pass into the blood stream and produce an endocarditis and sepsis which heal only rarely This clinical picture, the endocarditis lenta of the European school and the subacute bacterial endocarditis of the American students of the disease, is characterized by chronic mild fever, progressive anemia accompanied by a leukocytosis and occasional showers of large mononuclear cells, sometimes an enlarged spleen, changing cardiac murmurs, cachexia, positive blood culture and many embolic phenomena Particularly frequent is the embolic glomerulonephritis which occurs late in the course of the disease The body seems unable to offer any significant resistance in the form of immune bodies against this comparatively mildly virulent coccus, which hardly ever produces a purulent process

An important but unsettled problem is the question as to whether a mutability of these strains of Schottmuller takes place. Will *Streptococcus hemolyticus*, which has maintained its identity during cultivation under one set of conditions, change its characteristics to resemble those of a viridans, if the culture medium is changed, if the carbon dioxide tension is increased, or if the immune substances in the body in which it is growing are modified? More facts on this subject will have great significance for the pathologic study of the future.

Streptococcic infections often are the inciters of transient or persistent types of arthritis which closely resemble those seen in rheumatic fever. Inflammatory disturbances due to the streptococcus, with or without an accompanying arthritis or endocarditis, may originate in many parts of the body. Paessler of Dresden pointed out that the majority of those foci of infection are found in hollow spaces such as the gallbladder, urinary tract or thrombosed veins, or in semiquiescent abscesses which are not in direct relation with the living cells or with the circulating fluids of the body. It is not an uncommon experience to observe cases in which streptococci, having remained latent in such foci over a long period of years, suddenly invade the blood stream, producing a chill or fever. This picture is frequently seen in cases of septic thrombi, which often follow slight wounds, operation or unsterile intramuscular injections. But unquestionably the most important foci for the dissemination of the cocci are the tonsils and the infected apices of carious and devitalized teeth.

RHEUMATIC FEVER

When one leaves the field of the known etiologic factors in acute disease of the joints, one is struck by the fact that it is difficult to establish at the bedside a sharp line of classification that will differentiate between an arthritis due to a proved streptococcic infection and that caused by rheumatic fever. In fact, there are so many apparently transitional cases between true rheumatic fever and the mild cases of streptococcic sepsis that one must consider the possibility that rheumatic polyarthritis is only an attenuated form of streptococcic sepsis.

Jurgensen of Tübingen was the first to recognize rheumatic fever as a true infectious disease. In his further studies he found that a great many cases that he had previously believed to be rheumatic fever were in reality cases of sepsis caused by a cryptogenetic array of microorganisms. A group remained in which no causative agent for the polyarthritis could be found.

Undoubtedly, rheumatic fever is an infectious disease. Fiedler was one of the first observers to call attention to tonsillitis as a primary focus of infection for polyarthritis. This observation of Fiedler and of many

others has led to the approved procedure of extirpation of inflamed tonsils in patients with rheumatic fever as a prophylactic measure against subsequent lapses. Like many other observers, I have seen rapid recovery and cessation of relapses following the removal of infected tonsils in cases of rheumatic fever. But in many other such cases, tonsillectomy failed to modify the normal course of the disease. However, it is incorrect to assume that the tonsils are the only source of the infecting agent. Schottmuller has clearly demonstrated that in many such cases there may be secondary foci of infection in the veins or in the valves of the heart as well as in the tonsils. It follows naturally, therefore, that as little therapeutic result can be hoped for by the removal of only the infected tonsils in rheumatic fever when there are other active areas as might be expected from the extirpation of a chancre after the generalized distribution of the spirochete has taken place.

Experience has taught me to advise against tonsillectomy until all signs of tonsillitis have disappeared. When this warning has not been heeded, I have often seen an aggravation of the patient's illness, high temperature, and a pronounced albuminuria and hematuria. It would seem as if through the operative procedure bacteria were discharged into the circulation and thence to the kidneys. The same warning holds true for operations on the acutely inflamed nasal accessory sinuses, for I have seen cases in which sepsis and death followed too great an enthusiasm for early surgical intervention.

Typical rheumatic fever has been classified as a separate disease entity by McCallum, Hegeler and many others. Homer Swift has defined rheumatic fever "as a disease of undetermined etiology, characterized by the febrile state, by migratory inflammations of structure covered by serous membranes, by a peculiar inflammation of the myocardium and finally by the tendency for the febrile symptoms and arthritis to disappear following adequate doses of salicylates."

The disease begins most frequently between the tenth and the thirtieth year, and the great majority of patients have their first attack in the second decade. It is noteworthy that the younger the patient the greater the liability to endocarditis and chorea. This greater susceptibility to complications in the earlier years of life would seem to rest on the possibility that tissue reactions are a function of their age. Perhaps the richness in cells of the rapidly growing epiphysis increases the tendency of youth toward the infectious diseases of the bones and joints, such as tuberculosis and osteomyelitis.

Payr has argued that constitutional factors are important in the occurrence of rheumatic fever since there are so many instances of more than one case in the same family, as has been shown by Pribram,

St Lawrence, Faullenei and White, Draper and others. However, St Lawrence has shown from a parallel study of cases of rheumatic fever and tuberculosis that the conditions are of about the same magnitude in families. Since it is known that tuberculosis is an infectious disease, it might be argued that rheumatic fever is of the same nature, and it would be necessary to involve such factors as constitution to explain the high incidence of the disease in families.

However, many patients who have gout give a history of pains in the joints in their youth. I was previously of the opinion that this youthful condition was an early polyarticular form of gout. Experience taught me, however, that my previous belief was incorrect, for most of the patients who had gout, and who had suffered polyarthritis in their youth, had in reality passed through a siege of real rheumatic fever at that time. Perhaps one might predicate that in such cases there is a constitutional weakness of the joint structures, which in youth predisposes the patient to rheumatic fever and in later life to gout.

Furthermore, the occurrence of chorea with rheumatic fever is characteristic. It is noteworthy that this nervous complication practically always takes place in the second decade of life or in the first pregnancy of young women. It is then nearly always combined with a benign endocarditis.

Characteristically, the inflammatory process in the joints takes the form of a rapidly migrating polyarthritis. When one joint has apparently recovered, the infection may suddenly appear in another one. After a variable period of time, the swollen, painful joint will again approach its normal condition, and the complete restoration of function proves that the cartilages have remained intact. The inflammatory process is not limited to the synovial membrane, for the pronounced exudative and proliferative process also involves the periarticular connective tissues.

Unlike many other infectious diseases, rheumatic fever is characterized by a marked tendency toward relapses, which may possibly be due to the persistence of a latent focus of infection. It may take many years for a relapse to occur, for Mackie, at the Presbyterian Hospital in New York, has recently shown that "only 57 per cent of the first recurrences were found to develop within a period of four years following the first attack of rheumatic fever." Fiedler, Paessler and others have reported that in from 20 to 80 per cent of first attacks or relapses of rheumatic fever there was an associated tonsillitis. In my studies, this figure is about 50 per cent.

One of the frequent accompaniments of rheumatic fever is valvular endocarditis. Mackie found that there was a serious cardiac involve-

ment in 68 per cent of his 393 cases of rheumatic fever, irrespective of age. Other reports have placed the incidence nearer 35 per cent. However, Cohn and Swift have concluded from careful electrocardiographic studies that in thirty-five out of thirty-seven cases of rheumatic fever which they followed, the heart was involved in one way or another.

The pathologic condition in rheumatic endocarditis has been clearly described by McCallum, Libman and others. The mitral valve is most frequently involved, and the aortic is next in order. It is not an infrequent occurrence to find tricuspid or pulmonary rheumatic valvulitis. The pathologic picture of rheumatic endocarditis stands in marked contrast to *Streptococcus viridans* endocarditis. In the latter, large, soft, bead-like excrescences are found on the valves, the chordae tendineae and sometimes on the contiguous mural endocardium. The process in streptococcic infection is essentially of an ulcerative, destructive character. Minute aneurysms of the valves, leading to perforations, and friable, divided chordae tendineae are not uncommon in streptococcic endocarditis. In contrast to this picture, rheumatic endocarditis is characterized by a thickening due to cellular infiltration of the valves, sometimes followed by a proliferation of fine, wart-like verrucosities along the lines of closure of the valves. This process may proceed to a thickening and union of the valve cusps, and finally the valve orifice may so contract through the proliferative reaction as to produce a serious impediment to the natural course of the blood stream. McCallum has recently shown that the rheumatic inflammation frequently involves the mural endocardium of the left auricle. A curious whitish thickening extends from the posterior leaflet of the mitral valve along the auricular endocardium.

The myocarditis of rheumatic fever, however, is characterized by the presence of many noduli, which were first described by Aschoff. These cellular foci are found most frequently in the myocardium of the left ventricle in the vicinity of small arterioles. In the center of the nodule is a tiny area that takes stains poorly. It probably contains necrotic tissue and bits of fibrin. Clustered around this point in a thin meshwork of young fibroblasts, often in spindle-shaped form, is a collection of large cells containing one or many pale vesicular nuclei. Surrounding these so-called epithelioid cells is a zone containing lymphocytes, plasma cells, and occasional polymorphonuclear cells. Swift has described lesions of a similar nature in the synovial membrane of inflamed joints in rheumatic fever. He also believes that accumulations of cells reminiscent of Aschoff bodies may be made out in the subcutaneous nodules often seen in this disease.

Swift and other observers have felt that the response to the administration of salicylates is a characteristic feature of rheumatic fever. Many physicians will not agree with this point, for in many cases of severe rheumatic fever the salicylates have slight, if any, effect on the relief of pain and on inflammation of the joints. In such cases, I have sometimes observed that better results follow the administration of such pyrazolon derivatives as melubrin. A second proof that the salicylates do not act specifically against the cause of rheumatic fever is that they have no influence on the development of carditis, the liability of relapse, and the duration of the disease. Finally, the salicylates sometimes produce splendid therapeutic effects in gout, which obviously is unrelated to rheumatic fever.

Careful bacteriologic investigations have failed to disclose a specific etiologic agent for rheumatic fever. Schottmuller, Hegeler, McCallum and others maintain that the cause of the disease is unknown and that when a micro-organism is found in the blood stream or exudates of a patient with rheumatic fever it must be considered a secondary infection. It is true that when a bacterium, usually a streptococcus, is found in the blood of a patient who has previously had rheumatic fever, the clinical picture is usually that of endocarditis lenta. McCallum holds that the valves which have been thickened and shortened by the rheumatic fever process offer a point of vantage for further infection by secondary invading micro-organisms.

Although the pathologic picture of the endocarditis in rheumatic fever is so unlike that found in sepsis, in which a definite micro-organism is undoubtedly the causative factor, the clinical picture and course of rheumatic fever, with its early tonsillitis followed by inflammatory manifestations in such distant foci as the joints, the three layers of the heart, the pleura, etc., strongly suggest that an infectious agent has invaded the blood stream. In this regard, Clawson of Minneapolis and Small of Philadelphia have recently presented evidence that adds further plausibility to the fact that an anhemolytic streptococcus may be frequently present in the blood stream of patients with simple rheumatic fever.

Schottmuller has recently shown that the bacteria in the blood stream in cases of sepsis either are rapidly destroyed through the bactericidal properties of the blood serum, or are quickly taken up by the tissues of the body. A persistent bacteremia occurs only when the defensive mechanisms of the body have been reduced to a minimum. Such a condition does not, however, signify that the bacteria are growing in the blood, for their multiplication may be due to the fact that they are rapidly swept from the endocardial vegetations in which they are presumably growing luxuriously.

BACTERIOLOGIC INVESTIGATIONS

In recent years, Oeller, and Dietrich and Sigmund, his pupil, have studied the fate of bacteria which have reached the blood stream in disease processes and through experimental means. These workers found that when virulent micro-organisms were injected intravenously into animals, they were not demonstrable in the circulating blood after a relatively short period of time. Their rapid disappearance from the blood stream was due in part to the destructive action of the bactericidal substances of the blood, which were both specific and unspecific, in part also to the phagocytic action of the endothelial cells of the capillaries and venules. Shortly after the injection, the micro-organisms were found to have been carried into the adventitial spaces of the vascular channels. In the later stages of such cases, Dietrich and Sigmund showed the development of peculiar perivascular nodules which were made up in part of cells rich in protoplasm. These cells are the histiocytes, or the large macrophages of Metchnikoff, which are derived from the reticulo-endothelial system. Interspersed among the large wandering cells are polymorphonuclear leukocytes and lymphocytes. In the nodule, which bears a resemblance to a tubercle, the micro-organisms may undergo destruction through the agency of the cellular phagocytic elements. Roessle conceives of the inflammatory reaction as mainly a digestive process of the invading foreign bodies. Many years ago, I pointed out the digestive properties of the leukocytes and of the exudate in pneumonia.

It can be concluded that the absence of bacteria in the blood is therefore not a reliable sign that an invasion of the bacteria has not taken place at a previous time.

The little perivascular nodules described by Dietrich and Sigmund in such organs as the liver, spleen and lung manifest a striking histologic resemblance to the Aschoff bodies seen in rheumatic fever. If, furthermore, such "rheumatic nodules" can be demonstrated in severe forms of scarlet fever, those nodules cannot be considered as a pathognomonic sign of the specific nature of rheumatic fever.

In regard to the defensive mechanisms of the body against disease, the work of Theobald Smith on natural immunity is of great importance. He has shown that if new-born calves are deprived of the mother's first milk and therefore the colostrum, they succumb in a few days to a generalized *B. coli* septicemia. If, however, the calves are allowed to drink the colostrum immediately after birth, the *B. coli* sepsis does not take place, because the acquired immune bodies prevent the passage of the bacteria through the intestinal wall. If, on the other hand, the calves are not allowed to drink the colostrum

until a few days after birth, the delayed administration of protective substances gives them only an incomplete immunity and the animals develop a purulent polyarthritis. This is another example of the predilection that bacterial metastases have for the tissues of the joints.

The unspecific immunity with which the individual is endowed at birth, as well as the acquired immunity of the organism, may be so great that the invading bacteria are overcome at their entrance, and then the bacterium is avirulent for the body. In more serious forms of the disease, the invading power of the micro-organism is such that it passes into the blood stream and other tissues. The resisting forces of the individual may soon succeed in localizing the process, overcoming the invaders and causing a healing process. In the severest forms of infection, the immune agents of the body are unequal to the task of conquering the foe. The micro-organisms multiply in all the tissues, and the condition is described as sepsis.

This failure of the body to cope with the invading virus can be explained in two ways. It may be first argued that the micro-organism is possessed of particularly malignant toxic qualities. On the other hand, the results of animal experimentation and clinical observations have shown that the powers of immunity of a person may be seriously hampered or changed by certain poisons, roentgen-ray injuries, pregnancy and the effect of accompanying diseases, such as diabetes. One should therefore conceive of the virulence of a virus as dependent not only on the specific nature of the micro-organism but also on the powers of resistance of the body. It is to be emphasized that the term "virulence" is a relative matter, for a person who has long overcome a specific infection may finally succumb to it, since the effects of exhaustion or other diseases have produced a breakdown of resistance.

Complete healing takes place in many cases of rheumatic fever without any changes in either the joints or the valves of the heart. In other cases, the valves may become shortened and thickened and may remain in this fashion throughout the patient's life if there are no relapses. In some cases, however, the inflammatory process in the involved joint does not heal completely but persists as a mild, subacute or chronic polyarthritis. In the further development of such cases, periods of variable duration, characterized by tonsillitis, pain in the joints and fever, may occur. There is the possibility that each of these attacks records the entrance of a new crop of bacteria into the blood stream. In the later stages of this relapsing type of rheumatic fever, the symptoms in the joints fall into the background, and the clinical picture slowly begins to simulate that of a mild sepsis. Soon the temperature remains persistently high, the patient develops the profound pallor so aptly described as "café au lait," and the changing heart

murmers suggest that an active inflammatory process is taking place in the valves of the heart. The splenic tumor may sometimes be felt, and if blood cultures are carefully taken in the periods of highest fever a micro-organism, usually a streptococcus, may be recovered. Characteristic showers of emboli are thrown off from the ulcerated, infected valves of the heart. This leads to the production of multiple infarcts, especially in the spleen, kidneys and brain.

Is it really necessary for one to assume that in such cases a secondary invader of a particularly malignant character has engrafted a new infection on the valves already damaged in the inflammatory process of rheumatic fever? I believe that the slowly progressive history of such patients offers no basis for the opinion that the septic process is a secondary infection. I am of the opinion that the terminal process merely represents the results of the collapse of the resistive power of the individual against the same micro-organism which has been in his body for a long series of years. One must, therefore, consider the possibility that the infective agent, usually a streptococcus, which produces the terminal endocarditis, is the same as that which caused the repeated attacks of rheumatic fever in the patient's earlier life.

However, the data at hand are too meager to cause a denial of the possibility that a secondary infection with the streptococcus may not implant itself on the ground prepared for it by the unknown cause of the rheumatic fever in much the same fashion in which secondary *B. coli* infections follow the inflammatory tract paved by the gonococcus.

ACUTE ARTHRITIS

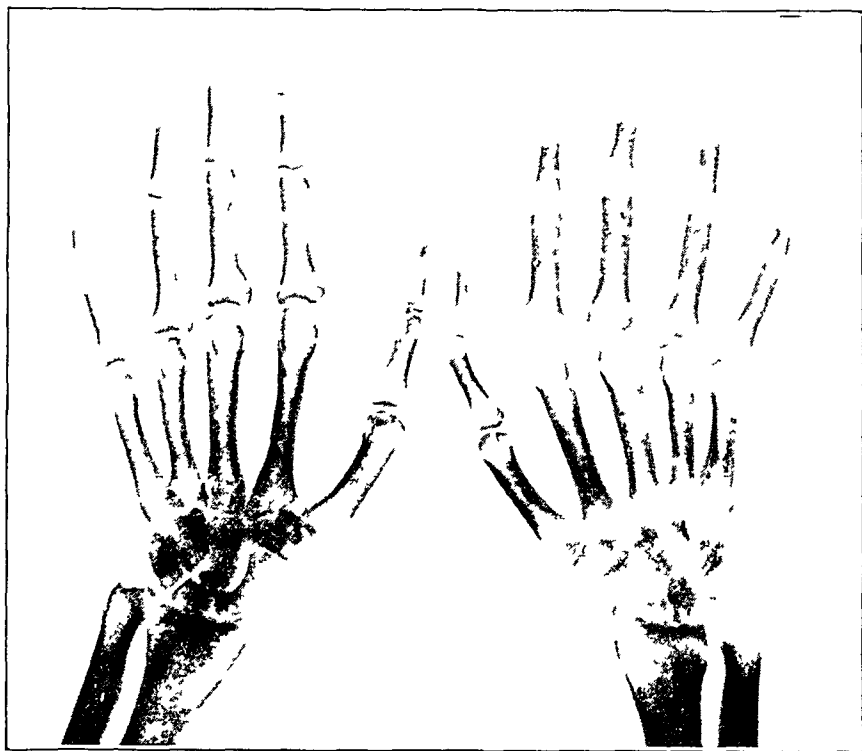
Another problem in general pathology of the joints is that of acute arthritis produced by toxic agents. It will be seen that the same type of destruction and ankylosis is present in the severe arthritides of gouty origin as in the pronounced cases of infectious arthritis.

In gout also, the attacks in the joints are of a true inflammatory nature. Exudation into the cavity of the joints is not uncommon, and in some cases this exudate was found rich in sodium urate, so rich in fact, that the supersaturated fluid withdrawn by puncture forms an abundant precipitate of fine crystals in needle-like form in the watch glass. There can be no doubt that the presence of the sodium urate solution is the source of the inflammatory reaction. I do not know how this accumulation of sodium urate in the joints takes place. Perhaps its source is the synovial membrane or the blood vessels of the subchondral epiphysis. The deposit of urate crystals is found on the surface of the cartilage covered by a thin layer of epichondrium.

Brositter, of this clinic, has shown that the sodium urate crystals are especially localized in little cup-like, punched out cavities of the

cartilage The urate deposits produce a local necrosis and destruction of the cartilage, which undergoes a remarkable type of disintegration and change in character. In the lower layers of the affected tissue a zone of calcareous deposit becomes visible, and young blood vessels and bone marrow cells grow into this primary calcification to produce a wart-like, osseous outgrowth. This new formation of bone is seen whenever destruction of cartilage occurs.

The diagnosis of a gouty condition of the joints often causes difficulty, because sometimes, especially in younger patients, the disease picture is primarily that of polyarthritis accompanied by pyrexia. In these cases of polyarticular gout, the diagnosis remains in doubt until



Appearance of hands in a case of gonorrheal arthritis, showing the characteristic hollow spaces of the epiphyses

the characteristic inflammation of the big toe appears or the blood uric acid value is abnormally high. In elderly patients, the clinical picture of gout may closely resemble that of arthritis deformans, but in most of these questionable cases the chemical examination of the blood serum determines the diagnosis.

It has been shown that an acute inflammation of the joints can occur in toxic as well as in infectious diseases. I shall now describe the chronic inflammatory process, but before entering into this discussion it will be necessary to define the expression "chronic inflammation."

"Chronic inflammation" describes an inflammatory process of long duration and not the permanent, inactive residue of an acute process.

Scar formation between two bones after an acute gonorrheal arthritis is not a chronic arthritis in the same sense that a mitral stenosis is not a chronic endocarditis. A chronic inflammation is therefore a *processus* and not a *status*. It is always the product of a long standing irritative agent. How can one explain the long duration of inflammatory processes of infectious or toxic origin?

I think it can be assumed that an acute inflammation is the product of a strong and vivid reaction of tissues against a noxious agent. This violent, acute reaction may result in complete recovery, but in some cases healing takes place with a permanent alteration in structure.

A chronic inflammation, however, is in most cases a mild reaction of long duration, which may be explained in two ways. The long drawn out struggle between the host and the invader is due to the fact either that the host is unable to produce a rapid reply to the invader or that the latter is so weak that it damages the host only to a slight extent. I believe that a combination of both these explanations should come into consideration.

The chronic infectious inflammations of the joints are nearly always characterized by slight elevations of temperature when a fresh involvement appears in a new joint. Relapses are frequent, but the attacks are rarely of a severe character. Sometimes the etiologic focus of the infection can be located in the tonsils, teeth, accessory nasal sinuses, appendix, or the genital tract. Elimination of the source of such foci of infection is not always possible, and even when the primary inflammatory area is disposed of, the progress of the arthritis is not necessarily arrested.

The chronic diseases of the joints of inflammatory nature are always characterized by a distinct atrophy of the epiphyseal osseous framework, and in some cases the diaphysis is involved in the same process. My own microscopic studies have not yet answered the question as to whether this atrophy is due only to inactivity or to chronic inflammatory processes in the bone marrow. In some of these cases, it has been possible to make out tiny foci of lymphocytic infiltration in the bone marrow. However, there is the possibility that the immobility of the limb which has caused the atrophy of the muscles may have caused the same changes in the bones discussed above.

It is interesting to observe that in true chronic infectious arthritis new osseous formations are seldom seen. Goldthwait is correct in his differentiation between the atrophic and hypertrophic forms of diseases of the joints. The chronic diseases of the joints of infectious origin belong, nearly always, to the atrophic type, whereas the chronic forms of gout are mostly of a hypertrophic character. Frequently, the cases of chronic infectious arthritis progress to a state of deformity and fixation of the joint.

The chronic infectious type of polyarthritis is frequently accompanied by some pathologic change of the heart or kidneys and is a serious condition. Continuous pain and progressive stiffness are present, and in later years anemia and cachexia may be prominent features. Among the chronic progressive inflammatory diseases of the joints is a type that begins acutely or subacutely, often runs a course characterized by relapses, and then shows a transition to a subacute polyarthritic form.

Another type begins as a chronic disease with mild swellings and pains of the finger joints, "*doigts en radis*," without a rise in temperature, and then slowly extends over more and more joints, deforming and stiffening them. I am not at all certain as to whether this second form is also of infectious character, and in most of these cases the origin of the disease remains completely in the dark. I must confess that this frequent form of the disease is the darkest part of the whole question.

I have seen cases in which the disease has affected nearly all the joints during the course of many years, but no signs of a severe alteration of the cartilages were demonstrable by the roentgen ray or autopsy. The mobility of the joints was slightly impaired, but the bones of the hands, feet, arms and legs were extraordinarily atrophic and showed only faint lines in the roentgenograms. The atrophy extended to the muscles, and the hands became transformed into useless, soft appendages. There were no signs of an inflammatory character or of osteomalacia. An anatomic preparation of the bones of such a hand was as light as a feather. I was at a loss to account for the etiology of this peculiar disease. I have seen two such cases in one family, so that perhaps constitutional factors are of importance in determining the susceptibility to the disease.

Among the chronic progressive diseases of the joints, one has also to consider those which are of toxic origin. The best known are ochronosis and gout. In ochronosis, the work of Virchow, Sir William Osler and other authors has shown that an autointoxication with dioxyphenylacetic acid leads to a brown discoloration and slow degeneration of all the cartilages of the body, including those of the ears. In Virchow's original case, the ligaments and fibrous tissues were of a brownish black. In connection with the degeneration of the cartilages, the epiphyseal portion of the bones may hypertrophy as in *athrophia deformans*.

Among the metabolic disorders, chronic uratic gout also can produce destruction and hyperplastic processes of the joints. It is sometimes difficult to find the characteristic accumulations of sodium urate. Munk believes that the hollow spaces shown by the roentgen ray in the epiphyses are characteristic of chronic gout, and our own anatomic

preparations have shown that these hollow areas in the epiphyses are filled with sodium urate and are surrounded by a mass of inflammatory cells. However, with Krebs, I have found similar hollow spaces in the epiphyses of chronic infectious arthritis in patients who have never had gout, and therefore these roentgen-ray examinations cannot be considered a reliable diagnostic feature of gouty accumulations.

It is astonishing to observe that there is less pain and inflammation in the chronic than in the acute attacks of gout. In chronic gout, huge concretions of urates may be present without producing either pain or inflammation. At one time it was thought that in chronic gout the tissues had become so accustomed and insensible to uric acid that sodium urate was no longer able to produce an inflammatory reaction. I tried to confirm this hypothesis by observing the results of subcutaneous injections of sodium urate. It was found that these injections produced the same degree of inflammation and pain in acute and chronic cases of gout, and more or less degree of inflammation in healthy, nongouty persons.

I was unable to detect a diminished reactivity or hypersensitivity of the gouty patients to these injections of sodium urate.

Chronic cases of gout sometimes produce hyperplastic processes of the bone near the cartilages. These excrescences on the fingers are the well known nodes of Heberden. This new formation of osseous tissue proximal to the injured cartilage is of great importance. It represents the same process that is seen in all cases of *arthropathia deformans*. The pathologic state of the cartilage must produce an irritation that results in the new formation of osseous tissue. This process is analogous to the formation of callus following a fracture of a bone. The callus with its spongy framework is produced by the periosteum, and its formation is especially abundant if a subperiosteal hemorrhage has occurred. It is therefore not surprising to find a proliferation of connective and osseous tissue follow traumatic injury of the joints. Hemorrhage into the cavities of the joints is also seen in hemophilia and in the attacks of *hydrops articulorum hypostrophos*. In all these cases, a hyperplasia of connective and osseous tissue is found.

Autopsies in cases of gout of long standing have shown true spur formation, and especially the milder forms of gout demonstrate a clear picture of hypertrophic osteopathy. These milder forms of gout, which are so common in old women in families in which gout is prevalent, are often overlooked and are diagnosed as *idiopathic arthropathia deformans*. The early history of the patient shows that he has previously suffered from typical attacks of gout. From my investigations, I can say that chronic forms of gout often produce the clinical and roentgen-ray pictures of *arthropathia deformans*. Of course, not all

cases of simple hypertrophic changes of the epiphysis and of Heberden's nodes are of gouty origin

The chronic proliferative forms of mild gout represent the transition to the second form of chronic diseases of the joints described by Virchow and Volkmann as *arthropathia deformans*. These investigators showed that this disease is of a productive and not of an inflammatory character, and that the first changes to be noted are the degenerations of the cartilages. Pommer of Innsbruck and Brogsitter of our clinic have confirmed these observations. All these workers agree that first a calcification and then a new growth of osseous tissue appears whenever a degeneration of cartilage takes place. This osseous hyperplasia occurs particularly on the edges of the cartilage to produce there the well known spurs which lead to a limitation of motion. Often the roentgenogram shows that the production of bony outgrowths is not limited to the region of the damaged cartilage, but extends to the neighboring structures. In such cases it would seem that there must be an irritation with a resulting productive activity in the periosteum. Often this hyperplastic process extends to the synovial membrane and produces polypoid excrescences of a villous character. It must therefore be concluded that the degeneration of the cartilage alone is not a sufficient explanation for the entire hypertrophic process.

Whenever the cartilage is entirely lost, the surfaces of the bones are exposed. Frequently, the cartilage of the opposite surface of the joint is also lost. The bones, therefore, begin to grind off in those places in which they are not protected by cartilage, and marked destruction and deformity of the surfaces result. No signs of inflammation are ever found on the unprotected bony surfaces, and therefore a proliferation of connective tissue never takes place. It is a rule without exception that ankylosis is never found in *arthropathia deformans*.

In consequence of the absence of inflammatory processes pain and swelling of the affected joint are not pronounced. The pain that is felt when the patient produces motion in the joint, as in standing or walking, is absent during rest. In the textbooks, advice is given to move the limbs because motion is said to prevent the progressive stiffening. It is questionable whether this treatment is correct. It may be more advisable to protect the joint against excessive movement and pressure, because overactivity on the part of the degenerated joint leads to increased malformation.

Often it is difficult to find the cause for the degeneration of the cartilage. It may be the simple senile atrophy of the cartilage with its subsequent mild bony hypertrophy which has been fully described by Weichselbaum and Pommer. Old age is a progressive and incurable disease, and so also are the senile conditions of the joints. In other

cases, the degeneration of the cartilage is due to mechanical causes. Malpositions of the lower limbs, such as flatfeet, coxa vara and genu valgum, are in later years often associated with arthritis deformans. In a similar manner, the latter may develop following fractures of the joints, old osteomyelites and tuberculosis of the joints.

In many cases, the origin of the arthropathia remains obscure. Chronic arthropathies often occur in the joints of the knees and hips of elderly women, and F Krause believed that this condition was related to an endocrine disturbance. Assmann strongly objected to this hypothesis. It is to be pointed out that in women many of these chronic degenerations of the joints may appear ten years before or ten years after the menopause. My observations seem to show that the arthropathy in such cases occurs almost always in obese women in whom a large excess of weight must be supported by the old joints in the legs. Favoring this point of view is the fact that a reduction in weight is the best therapy in this form of disease of the joints. I do not wish to deny that endocrine disturbances may produce chronic conditions of the bones. Rothschild and Dewy have described such conditions accompanying pathologic states of the thyroid gland, and not unfrequently I, too, have seen such cases. In these patients the administration of desiccated thyroid gland has produced a good therapeutic effect. The same satisfactory results often follow thyroid treatment in the involvements of the joints that are sometimes combined with scleroderma. The disturbance in the joints in scleroderma sometimes presents the picture of the so-called calcareous gout. In some cases of osteomalacia not only the bones but also the joints are affected, and there can be no doubt that this disease is of endocrine origin.

One of the most typical forms of arthropathia deformans is "malum coxae senile." Here also the disease begins with degeneration of the cartilage. The bone of the caput femoris and the acetabulum are exposed, their surfaces are ground away, and the resulting new formation of bone tissue produces an excessive deformation which extends to the collum and even to the trochanter. In most cases of malum coxae senile, the patient complains of pain only in one side, but when the motility of the opposite hip joint is examined thoroughly, it also is nearly always found to be affected. Often the roentgen-ray studies demonstrate accompanying deformities in the knee, shoulder and fingers. It therefore seems probable that a constitutional and not a mechanical factor alone plays a part in this disease.

Charcot's disease of the joints or "arthropathia tabidorum" also belongs to the category of hypertrophic arthropathies. The involvement of the joints in tabes and syringomyelia shows the same excessive new formation of bone together with a severe destruction of the cartilages.

Sometimes the enlarged knee or ankle joint looks as if it had been shattered to pieces by a severe blow with a hammer. Some neurologists believe that Charcot's disease is due to the degeneration of the trophic nerves to the bones, but I believe that a simpler explanation is possible. The condition of the joints in tabes and syringomyelia is characterized clinically by a complete absence of pain. One may move the severely involved joint in all abnormal directions without producing the slightest pain and even without the patient's knowledge. The absolute loss of sensibility and pain in the joint may lead to overstrain, to damage, and even to fractures, and since the patient is deprived of warnings by pain, he uses and insults his damaged joint so as to make the injury progressively worse.

Assmann believes that the spontaneous fractures of the bones which occur in tabes cannot be explained by the loss of pain alone, rather that they indicate a definite alteration in the bones themselves. If this is true, it must be concluded that the diseases of the joints in tabes are due to a primary involvement of the bones rather than of the cartilages. However, I have never seen atrophic disturbances of the bones in tabes. Indeed, many diseases of the joints have their primary origin in the bones. For example, the involvement of the joints in tuberculosis, osteomyelitis and metastatic tumors is usually secondary to a primary involvement of the bone. I have seen a case of hemolytic icterus in which splenectomy had been practiced with excellent results. After several years, a severe destruction of the hip joint appeared, producing a picture similar to tuberculosis. The microscopic examination of the spleen showed that it was not a simple case of hemolytic icterus or Banti's disease, for the splenic sinusoids were filled with the large cells characteristic of Gaucher's disease. Pick of Berlin has seen similar cases of Gaucher's disease with metastatic processes in the bone producing secondary changes in the joint.

It can therefore be seen that pathologic conditions of many kinds are able to localize in the bones and joints and that one has to take a much broader view of diseases of the joints than before. Microscopic, bacteriologic and clinical investigations must be combined for the further study of this important field.

CONTRACTIONS OF GALLBLADDER SEEN IN MAN

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Broadly, the pitfalls of scientific procedure are fourfold, as is shown when an endeavor is made to answer the following questions 1 Are all the necessary phenomena accurately observed? 2 Are all the phenomena relevant to the problem under consideration? 3 Are all the phenomena irrelevant to the problem eliminated? 4 Has the actual sequence or interrelation of phenomena been established?

These difficulties are common to both observation and experiment, but each of these methods also has defects and advantages which are peculiar to itself According to John Stuart Mill ¹

The first and most obvious distinction between Observation and Experiment is, that the latter is an immense extension of the former It not only enables us to produce a much greater number of variations in the circumstances than nature spontaneously offers, but also, in thousands of cases, to produce the precise sort of variation which we are in want of for discovering the law of the phenomenon

When we can produce a phenomenon artificially we can take it, as it were, home with us, and observe it in the midst of circumstances with which in all other respects, we are accurately acquainted

In the field of the physiology of the gallbladder, as in all biologic investigation, it is, of course, rarely possible to be accurately acquainted with all the circumstances attending an experiment There is so little precise knowledge of the effects of anesthetics and surgical procedures on the organism, not to mention the unknown factors, that the conclusions drawn from experiments which depend on these must be taken critically

Observation, then, has this advantage, that it requires the least tampering with the natural process Of course, the danger of overlooking some significant circumstance will remain until everything is known, but then what need will there be for investigation? Nevertheless, these two methods are the legs on which science has made every advance One can only gratefully avail himself of every opportunity for observation and experiment and keep a watchful eye on the dangers that lurk in half knowledge

Recent progress in the knowledge of the physiology of the gallbladder bears witness to the value of the experimental method in the medical

1 Mill, J Stuart Logic, New York, Harper and Brothers, ed 8, 272

sciences The names of Rous, McMaster, Burget, Boyden, Ciohn, Winklestein, Aschner, Diamond, Higgins, Mann and Whitaker represent a valiant effort to discover the workings of the gallbladder However, observation as a method had no place in the investigation of this organ, because it could not be observed under normal conditions The frequent exposures of the gallbladder by the surgeon did not offer satisfactory opportunities for observation, since a laparotomized man is no more fit to be the object of observation than an experimental animal so treated Under such conditions man becomes the unintended object of an experiment, and subject to all the new factors, known and unknown, thus introduced This was recognized by Mann,² who said

In our experiments as well as in all operations on the biliary tract caution is necessary in drawing conclusions because the possibility of trauma or pressure of a foreign body will greatly disturb the normal action of the gallbladder

Whitaker,³ in his experiments on cats, observed that

The physical condition of the subject seemed to be an important factor, if he were ill no emptying might occur after feeding, or the attempts were feeble This would indicate that results obtained by any experimental method in which the condition of the animal was not normal, would be open to question

It was not until Graham and Cole⁴ introduced their method of cholecystography that an opportunity was offered to the clinician, who is essentially an observer, to add to the knowledge of the physiology of this organ Up to 1924, the normal gallbladder was terra incognita to the clinician Only when enlarged, thickened, or filled with stones was there any hope of seeing it, and then only in rare and fortunate cases⁵ But Graham and Cole have made it possible to study this organ in its normal state, to note its shape, position, density and emptying time This is a boon to the clinician interested in his calling and increases the number of investigators of this organ from a few laboratory workers to a host of clinicians and roentgenologists

Unfortunately, the experimental method, at least as applied to the gallbladder, has as yet not brought forward any conclusive results This is illustrated by the lack of unanimity among experimenters concerning

2 Mann A Physiologic Consideration of the Gallbladder, J A M A **83** 829 (Sept 13) 1924

3 Whitaker Am J Physiol **78** 411, 1926

4 Graham and Cole Roentgenologic Examination of the Gallbladder, J A M A **82** 613 (Feb 23) 1924

5 Assmann Die klinische Röntgendiagnostik der innern Erkrankungen, Leipzig, F C W Vogel, 1924, p 703

some of its most vital problems, as shown by their replies to the following questions

Does the gallbladder contract to expel the bile?

<i>Yes</i>	<i>No</i>
Whitaker ³	Graham ¹⁰
Higgins and Mann ⁶	Winklestein and Aschner ¹¹
Ellman and McMaster ⁷	
Chiray and Pavel ⁸	
Meltzer ⁹	

Does an artificial gallbladder empty itself?

<i>Yes</i>	<i>No</i>
Graham ¹⁰	Whitaker ³

Do respiratory movements influence the emptying of the gallbladder?

<i>Yes</i>	<i>No</i>
Winklestein and Aschner ¹¹	Whitaker ³
	Higgins and Mann ⁶

Does the flow of bile from the liver through the common duct exert a siphonage action on the gallbladder?

<i>Yes</i>	<i>No</i>
Graham ¹⁰	Whitaker ³
	Higgins and Mann ⁶

Is the empty gallbladder flaccid or contracted?

<i>Contracted</i>	<i>Flaccid</i>
Higgins and Mann ⁶	Graham ¹⁰

Do duodenal peristalsis and tonus affect the flow of bile from the gallbladder?

<i>Yes</i>	<i>No</i>
Burget ¹	Whitaker ³
Copher and Kadama ¹³	

Does the presence of acid in the stomach increase the flow of bile?

<i>Yes</i>	<i>No</i>
Ellman and McMaster ⁷	Whitaker ³
Cole ¹⁴	Bruns ¹⁵

Does the presence of food in the stomach induce the emptying of the gallbladder?

<i>Yes</i>	<i>No</i>
Cole ¹⁴	Whitaker ³

6 Higgins and Mann Am J Physiol **78** 339, 1926

7 Ellman and McMaster J Exper Med **44** 151, 1926

8 Chiray and Pavel Am J M Sc **172** 11, 1926

9 Meltzer Am J M Sc **153** 469, 1917

10 Graham Am J M Sc **172** 625, 1926

11 Winkelstein and Aschner Am J M Sc **171** 104, 1926

12 Burget Am J Physiol **74** 583, 1925

13 Copher and Kadama Regulation of Flow of Bile and Pancreatic Juice Into Duodenum, Arch Int Med **38** 647 (Nov) 1926

14 Cole Am J Physiol **72** 39, 1925

15 Bruns, quoted by Howell Text-Book of Physiology, Philadelphia, W B Saunders & Company, 1922, p 817

What is the role of the sphincter of Oddi in the emptying of the gallbladder?

Important

Meltzer⁹

Chiray and Pavel⁸

Ellman and McMaster¹¹

Unimportant

Whitaker³

Copher and Kadama¹³

Higgins and Mann⁶

Graham¹⁰

Burget¹²



Fig 1—Taken before the administration of the dye (tetraiodophenolphthalein)
The gallbladder is not visible

It is evident that additional information is necessary before these problems can be solved satisfactorily. Some of them are beyond the range of the clinician. Others are within his sphere and should be given proper attention.

16 Ellman and McMaster (footnote 7) "We attribute the sudden changes chiefly to the activity of the sphincter of Oddi."

Of the foregoing problems, the most important and the most pressing is the question of whether or not the gallbladder expels the bile by the contractile force of its own musculature. Higgins and Mann⁶ have observed localized contractions in the exposed gallbladders of guinea-pigs. Whitaker³ performed experiments in which iodized oil was introduced into the gallbladder of cats and the abdominal wound was closed. After fasting for twenty-four hours, the animal was given a meal rich in fat, and the gallbladder was examined under the 10 centgen ray. Marked

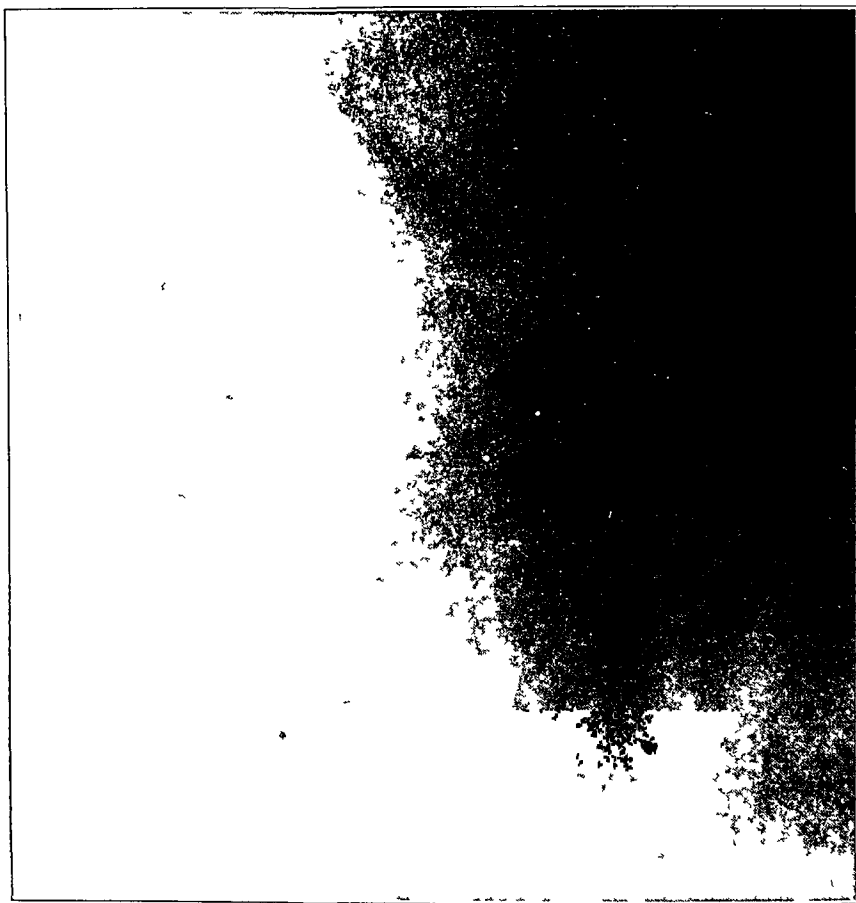


Fig 2—Figures 2, 3 and 4 were taken fourteen hours after the administration of the dye by mouth. The gallbladder is visible. Its lower pole is oval.

changes were observed in the shape of the gallbladder during the process of emptying.

I studied the gallbladder of a man, a physician, who fourteen hours after the administration of the dye (tetraiodophenolphthalein) by mouth, showed an oval gallbladder (figs 2, 3 and 4). Two hours after the administration of a meal rich in fat, marked changes were noted in its contour, indicating active contractions in its wall. These changes showed a striking similarity to those in Whitaker's experiment. (Compare figures 5, 6 and 7 with figure 8.) These 10 centgenograms also

illustrate the observations of Higgins and Mann⁶ on the exposed gallbladder of the guinea-pig I quote from these authors

The exposed vesicle at the beginning of observation is usually spherical. Instead of reducing as a unit as a urinary bladder does in expelling its contents, independent centers of contraction induce a variety of patterns in the emptying vesicle. There are no waves of contraction, extending over the fundus and



Fig. 3—Taken fourteen hours after the administration of the dye by mouth

on to the neck of the bladder but only these localized contractile areas. Very frequently we have observed contraction of these regions to form small knoblike diverticula over the entire fundus.

REPORT OF A CASE

History—L. K., aged 43, a physician, gave a family history which was irrelevant. His wife and two children were alive and well. He drank one cup of coffee a day and an occasional cup of tea. He did not use alcohol and smoked

fifteen cigarettes a day. He had had the usual diseases of childhood. Up to ten years before presentation, he had had an acute attack of tonsillitis yearly. Since then, he had had only two or three attacks. The tonsils had not been removed. He had not had pneumonia, typhoid, malaria, acute rheumatic fever, any operations or accidents. The present illness began when he was 12 years of age, and since then he had been subject to heart burn. Mucus was present in the stool at the age of 15. This condition lasted five years. When 19 years of age, he first noted a lumpy feeling in the epigastrium and between the scapulae, which lasted

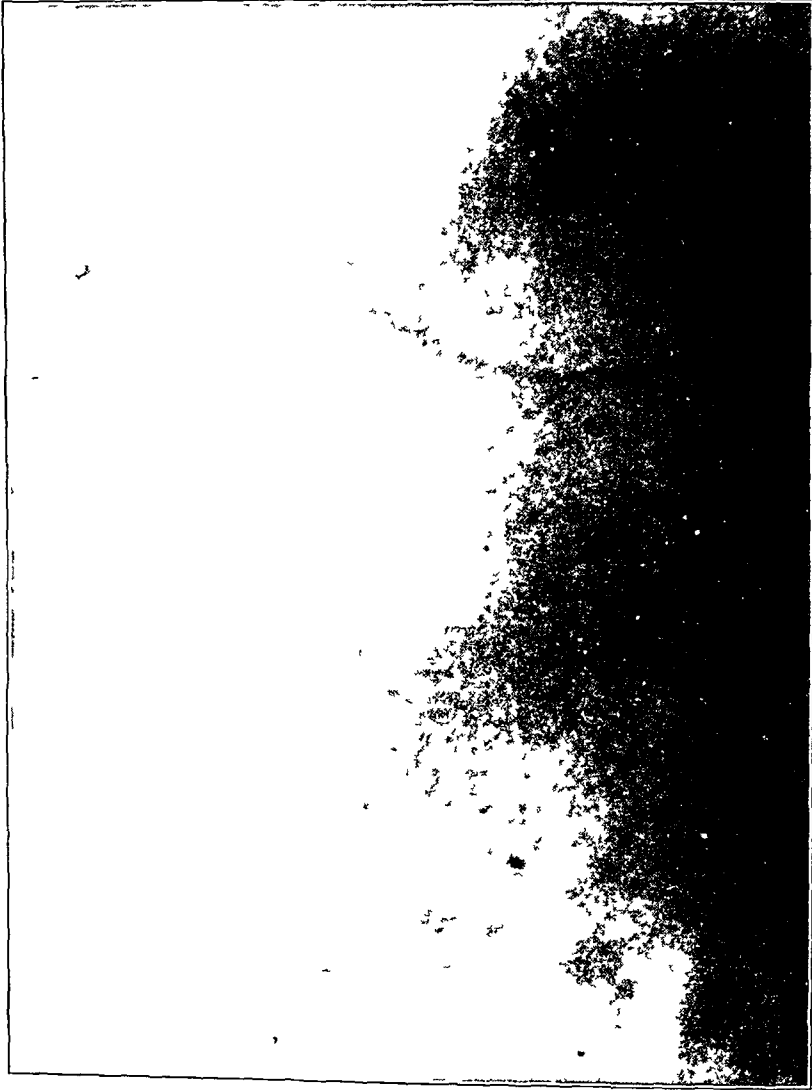


Fig 4—Taken fourteen hours after the administration of the dye by mouth

a few days. He described the sensation as extremely uncomfortable but not exactly painful. The heart burn has continued up to the present, and is not relieved by food, in fact, it is even aggravated by it. Immediate relief is obtained from sodium bicarbonate or magnesia magma.

On Jan 1, 1918, when the street car on which he was riding made a sharp turn, the patient experienced a sudden, agonizing pain in the epigastrium which radiated straight back. Similar attacks had occurred at intervals varying from once in three days to once in six weeks. They occurred most often two or three

hours after meals, occasionally before meals, and were promptly relieved by alkalis. In fact, the patient had been able to ward off an attack by means of alkalis if taken soon enough. The attacks had lasted from one to forty-five minutes and were not relieved by movement of the bowels or the passage of gas. The pain had awakened him at night only once, five years ago. A sense of pressure in the epigastrium and in the rectum and a desire to urinate accompanied the attacks, the patient belched a good deal after the attack subsided and felt perfectly well within two minutes after it had passed. His appetite was good, his weight was stationary and he had never vomited during or between the attacks. The bowels moved daily, but the movement was constipated. The patient took an occasional mild laxative. About six months before presentation he noticed a few drops of blood on the stool after a large movement.



Fig 5—Figures 5, 6 and 7 were taken two hours after the administration of a meal rich in fat. The gallbladder is flattened at its base and distended from side to side. At its outer border a protrusion appears in the same location as that seen on the gallbladder of Whitaker's cat. This is most marked on figure 5, less marked on figure 6, and on figure 7, the outer border is almost round.

Nocturia, frequency, dysuria, cough nor dyspnea on exertion had not been noted. The patient has not had headache or dizziness, the vision is fine and he sleeps well. He was never jaundiced.

Examination—The pulse rate was 72 and regular. The blood pressure was 122 systolic and 82 diastolic on the left arm, and 102 systolic and 86 diastolic on the right arm. The patient weighed 160 pounds (72.6 Kg). The teeth were in poor condition. The throat was congested, and there was granular pharyngitis. The lungs and the heart did not reveal any pathologic conditions.

The determination of the right Boas point was positive. The liver and spleen were not palpable. The entire right side of the abdomen was tender, but tenderness was most marked in the region of the gallbladder. The gallbladder was not palpable and rocking liver elicited much pain. Pressure over the area of the gallbladder gave the patient the same painful sensation as that experienced during the attacks.

The results of the rectal examination were negative.

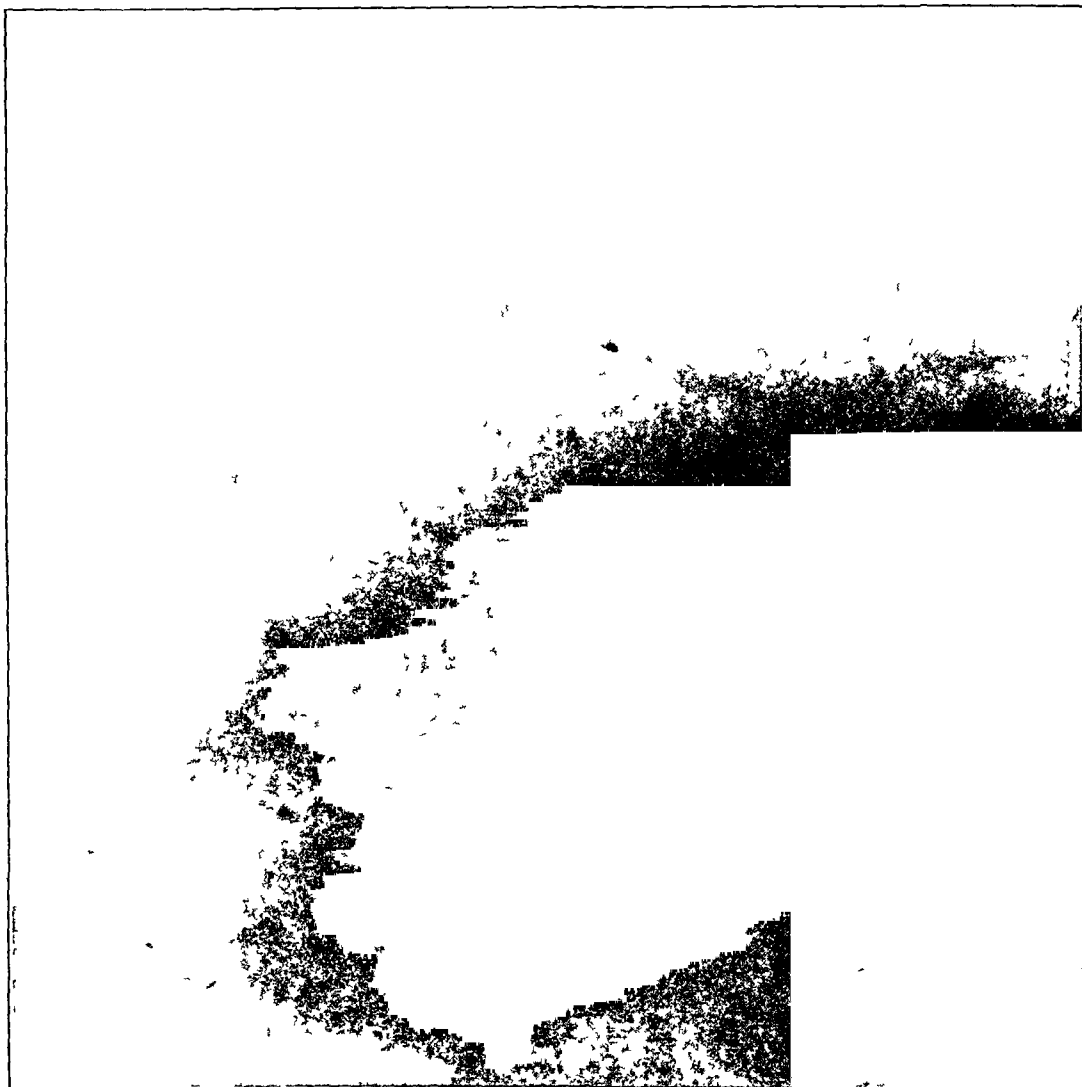


Fig 6—Taken two hours after the administration of a meal rich in fat

An examination of two specimens of the feces revealed an alkaline reaction, the benzidine test for blood was negative, no ova were found. Urinalysis was negative.

Chemical examination of the blood showed sugar, 93 mg, creatinine, 12 mg, urea nitrogen, 12.5 mg, icteric index, 88, blood bilirubin, $\frac{1}{200,000}$. The blood Wassermann reaction was negative. The blood count revealed 5,850,000 red blood cells, 76 per cent hemoglobin (Sahli) and 7,400 white blood cells. The differential count showed 59 per cent polymorphonuclear leukocytes, 39 per cent small and

large lymphocytes, 2 per cent eosinophils. An examination of the gastric contents revealed residue, 12 cc of clear fluid, free hydrochloric acid, 34, total acidity, 48, negative blood and bile.

A fractional test meal (Rehfuss) was given. The first specimen was removed fifteen minutes after administration of the test meal.

A M	cc	Free Hydrochloric Acid	Total Acidity
1—10 00	20	13	30
2—10 15	22	12	36
3—10 30	20	16	49
4—10 45	20	18	50
5—11 00	40	44	66
6—11 15	20	62	78
7—11 30	20	45	65
8—11 45	20	25	34

A test meal of barium gruel was administered before breakfast. Fluoroscopy of the stomach did not reveal any obstruction in the esophagus. The lowest point of the greater curvature extended two fingerbreadths below the crest of the ilium. The incisura angularis was on a level with the crest. The pylorus did not extend beyond the right border of the spine, was tonic in type and the shape of a fish hook. Peristalsis, time required for emptying, indentations, fluid layer and air bubble were normal. Niches, defects or tenderness were not noted. The duodenal cap was small and triangular, and the apex was directed upward and the base downward. Niches or defects were not seen. Pressure over it did not elicit tenderness, but there was marked tenderness when pressure was applied above it, in the area of the gallbladder. The duodenal loop was not enlarged. Angulations were not present. The foregoing observations were corroborated on the roentgenograms of the stomach and the duodenum.

After four hours, the stomach was empty. The head of the barium meal was in the ascending colon, the remainder in the ileum.

After twenty-four hours, the barium occupied the large intestine from the cecum to the middle of the transverse colon. The appendix was filled and was irregular in outline and beaded. Its direction was upward and to the left, and then transversely to the left.

After forty-eight hours the barium was seen in the large intestine from the hepatic flexure to the pelvic colon. The cecum and the ascending colon were empty, but the appendix was still filled and was irregular and beaded. Its direction was downward and to the left.

After eighty-four hours, only a thin layer of barium could be seen in the distal colon, but the distal portion of the appendix was still filled with barium.

A barium enema was given, the entire large intestine readily filling from the rectum to the cecum. A little barium entered the ileum. The splenic flexure reached up to a little above the lower border of the heart. The hepatic flexure reached up to costal margin. There was considerable spasm in the descending colon and the sigmoid.

Proctoscopy was performed, the proctoscope entering 30 cm. Considerable congestion was noted in the mucous membrane of the sigmoid.

There were no pathologic conditions in the heart or the lungs. Roentgenograms showed the gallbladder clearly fourteen hours after the administration of the dye (tetraiodophenolphthalein) by mouth. Its lower pole was rounded on all three roentgenograms (figs 2, 3 and 4). Two hours after the administration of a meal rich in fat the gallbladder had hardly diminished in size. Its lower pole was no longer rounded but flattened from above downward, and distended from side to side. A protrusion was clearly seen at its outer border (fig 5). This assumed a more rounded shape in figures 6 and 7.

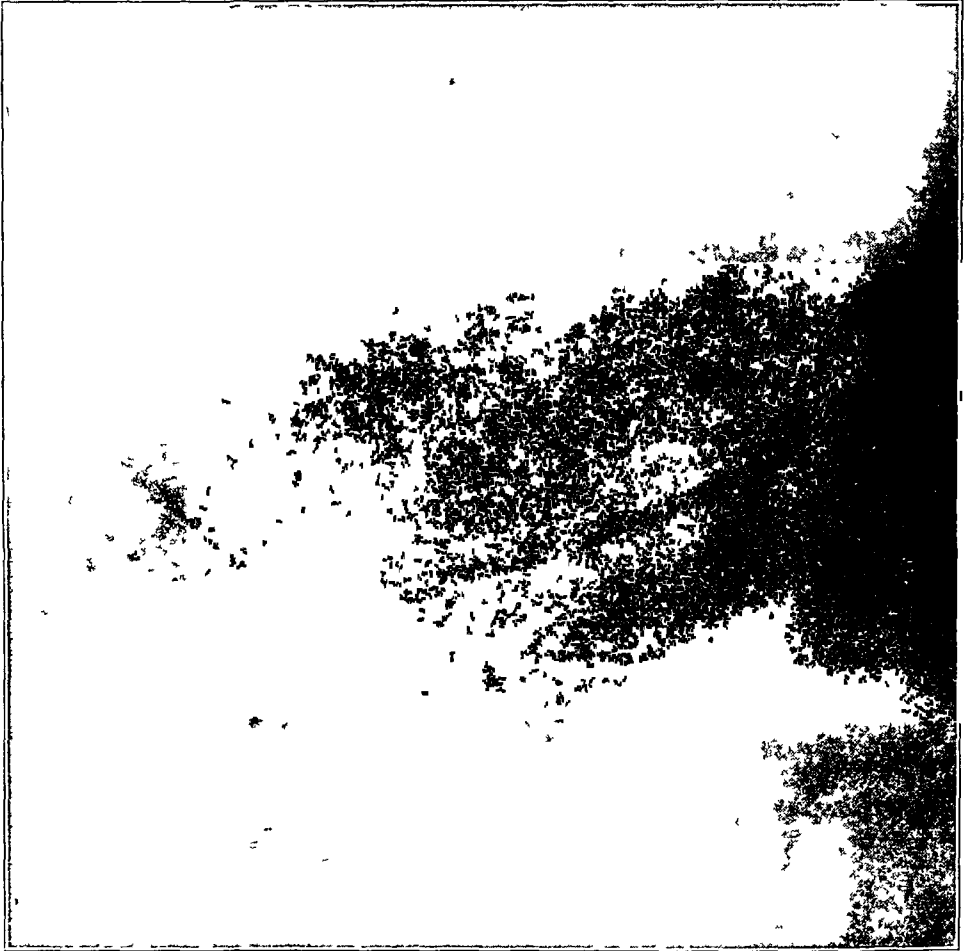


Fig 7—Taken two hours after the administration of a meal rich in fat

COMMENT

Changes in the shape of a hollow organ may be produced in three ways (1) by pressure or release of pressure from within, (2) by pressure exerted on it from without, and (3) by the contraction of its own walls.

Hydrostatic laws rule out the first possibility (Pascal's principle). Any horizontal layer in the gallbladder has the same pressure of bile at all its points; therefore the release of the pressure should affect all its



Fig 8—Copy of the gallbladder of Whitaker's cat Compare this with figures 5, 6 and 7, and note the similarity (from Am J Physiol **78** 415, 1926)

parts proportionately. The result should be a uniform collapse of the gallbladder. Instead there are flattened areas in some places and bulging in others.

Winklestein and Aschner¹¹ offered the second hypothesis. They are of the opinion that the descent of the diaphragm during inspiration exerts sufficient pressure on the gallbladder to "squeeze" the bile into the common duct. From figures 2, 3 and 4, however, it is readily seen that there was no change in the shape of the gallbladder before the administration of the test meal, though obviously respiration was going on at that time. Not until after the administration of a fat meal, which induces the emptying of its contents, were definite changes in its shape observed (figs 5, 6 and 7). Besides, roentgenograms of the gallbladder are always taken during expiration. The experiments of Whitaker³ and of Higgins and Mann⁶ have, moreover, conclusively disproved this theory.

There remains only the last hypothesis, that the observed changes in the shape of the gallbladder are caused by contraction of its walls. Figures 5, 6 and 7 show flattening of certain areas with compensatory bulgings in others. Changes are observed exactly analogous to the "localized contractions" described by Higgins and Mann in their experiment.

Obviously the gallbladder that I observed was not normal, since it had hardly diminished in size two hours after the fat meal was given. To what extent may these changes in shape be due to its pathologic condition? That these changes were not caused by thickening of its walls or pericholecystic adhesions is evident from the fact that they do not appear in the earlier roentgenograms when the bile was confined within the interior of the gallbladder. They appear only after the meal of fat which induced the flow of bile into the duodenum.

The question arises. Why have not these changes been observed more often? In the first place, roentgenograms after a test meal are taken at a time when the gallbladder is greatly reduced in size, and changes in its contour are not easily detected. This gallbladder, on the contrary, had not diminished in size two hours after the test meal, thus furnishing an opportunity for observing its efforts to empty itself. It is also likely that its abnormal state calls forth an increased effort on its part to expel the contents. A calculus, a stricture or any obstruction at its outlet would accentuate its normal contractions and make them visible. If, on the other hand, contractions did not occur normally, it is hardly likely that it would contract when diseased. However, it must be admitted that since the exact condition of this gallbladder was not known, the reason why the contractions were observed in this case must be largely speculative.

SUMMARY

1 Graham and Cole, by their method of cholecystography, have given clinicians a means of observing the gallbladder without the introduction of new factors which may modify its behavior

2 The conclusions on the physiology of the gallbladder reached by experiments are open to the objection that abnormal conditions, such as the effects of anesthetics and operative procedures, are introduced

3 Both observation and experiment are valuable but should be taken in conjunction to supplement and correct each other

4 A case has been described in which changes strongly suggestive of contractions were observed in the gallbladder of a man two hours after the administration of the fat meal. These changes closely resembled those observed by Whitaker³ in the gallbladders of cats at the time when they were discharging their contents. They also correspond to the description given by Higgins and Mann⁶ of the exposed gallbladders of guinea-pigs while undergoing active contractions

5 The fact that the gallbladder under observation was apparently pathologic does not seem to vitiate the conclusion that the normal gallbladder undergoes contraction at the time when it empties its contents

EFFECT OF EXPERIMENTAL PYLORIC STENOSIS ON GASTRIC SECRETION *

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An increase above the normal average in the acidity of the gastric contents is observed in various conditions associated with pyloric obstruction in man. This condition is referred to as "hypersecretion and hyperacidity." In most cases, however, the amount of acidity, although greater than the normal average, is within the limits of normal variation. Therefore, in the absence of a knowledge of the acidity of the gastric contents prior to the onset of the disease causing the pyloric obstruction, it may be argued that the acidity found is normal. Also, since there is usually a gastric retention in pyloric obstruction due to functional or organic disturbances, it is probable that a hypernormal acidity may be due to a retention of a normal amount of gastric secretion, and therefore is only relative. Even if hypernormal secretion did occur, one would not be able to state whether it was due to the obstruction and retention per se or to the disease causing the obstruction.

In considering whether or not pyloric obstruction causes "hypersecretion and hyperacidity," one must distinguish between a relative and an absolute hypernormal secretion and acidity. In relative hypernormal secretion and acidity, the condition would be due to retention of gastric secretion and therefore only apparent, in absolute hypernormal secretion and acidity, the condition would be due to an actual increase in the amount and the acidity of the secretion produced. A gastric analysis in the presence of gastric retention is not an accurate measure of the quantity and quality of the juice secreted. A method is not known whereby one can measure accurately the secretion that is being formed when food is in the stomach. Not even the Pawlow pouch reflects all the secretion that is going on in the stomach during a meal. If the interdigestive or the continuous secretion in patients were observed, which should be done more commonly for scientific purposes, significant figures of hypernormal secretion and hyperacidity might be obtained, but then one would be studying only the intestinal phase of gastric secretion, and the data would not be conclusive unless the interdigestive secretion was studied prior to the onset of the disease.

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Hamburger and Friedman¹ have studied the effect of "uncomplicated" pyloric stenosis experimentally produced in dogs by placing a silk ligature about the pyloric outlet. In order to determine gastric acidity and volume, they caused vomiting by the administration of apomorphine from fifty to sixty minutes after feeding the dogs with a test meal, they then determined the quantity and acidity of the vomitus. They found that moderate stenosis produced little if any change, and that marked stenosis caused retention and hyperacidity, they therefore concluded that the hyperacidity was due to hypersecretion. Such a conclusion is hardly warranted in view of the foregoing facts.

At present, there is no ideal method for the study of the effect of pyloric stenosis on gastric secretion. Production of the Pawlow pouch is the best method to use, but in using the Pawlow pouch, it must be kept in mind that it responds poorly when the stomach proper is distended mechanically,² and hence will only partly reflect the mechanical effect of retention by the stomach.

METHODS

A Pawlow pouch was made in twelve dogs by the usual technic. From five to ten control responses were obtained to a standard meal consisting of 200 Gm of ground meat, 250 cc of milk and 100 Gm of bread mixed thoroughly. In the first eight dogs the secretion was collected during two one hour periods prior to the meal, for from three to six hours after the meal and, in a few instances, for twenty-four hours after the meal. As most of the tests made on the first eight dogs were continued for three hours after the meal, the figures given in the tables (tables 1, 2, 3, 4 and 5) are for a three hour period following the meal. In the other four dogs the secretion was collected from six to twenty-four hours after the meal. The results shown in the tables (tables 6 and 7) are for a ten hour period following the meal.

In some cases stenosis was produced by tying a tape a quarter of an inch wide about the pyloric sphincter, in others, by placing an aluminum or silver band a quarter of an inch wide about the pyloric sphincter. Bands of different sizes were prepared in order that they might be accommodated to sphincters of different sizes. The band was placed snugly, but not tightly, about the sphincter. Our desire was to produce a partial stenosis that would lead to a retention of from two to four hours, we were not able to obtain such a result, however.

The degree of stenosis obtained was ascertained by determining fluoroscopically the emptying time before and after the stenosis was made. In the first eight dogs, the exact emptying time after the production of the stenosis was not determined, because the animals had to be transferred some distance before the fluoroscopic examination could be made. To determine whether there was retention, we made a fluoroscopic examination of the animals at the time their stomachs would normally be empty, and expressed the results as "retention,"

1 Hamburger, W. W., and Friedman, J. C. Contributions to the Experimental Pathology of the Stomach, *Arch. Int. Med.* **14**: 722 (Nov. 15) 1914.

2 Lim, Ivy and McCarthy. *Quart. J. Exper. Physiol.* **15**: 13, 1925.

"marked retention" and "high grade retention," according to the amount of material in the stomach

For a few days after the stenosis was made, the animal was given only water, meat broth and milk with bread crumbs in small portions until it was found that the standard meal could be ingested without provoking vomiting

RESULTS

A pyloric stenosis was produced in twelve dogs with a Pawlow pouch. Seven of the twelve lived long enough to give responses to the standard meal, six of the seven were observed for from three and one-half to

TABLE 1—*Effect of Pyloric Stenosis on Gastric Secretion*
Dog 2* with a Pawlow pouch

Procedure	Amount in Cc	Free Acidity	Total Acidity	Comment
Control Period				
May 19	19.5	0.41	0.45	
20	28.5	0.45	0.51	
21	17.0	0.37	0.44	
22	12.0	0.40	0.48	
23	19.0	0.41	0.45	
24	16.0	0.39	0.47	
25	16.5	0.35	0.40	
Pyloric stenosis produced with tape, May 25				
May 27	6.0	0.29	0.31	Vomited water but not meat
28	4.0	0.32	0.40	
29	5.0	0.43	0.47	No vomiting
31	7.5	0.14	0.20	
June 2	6.5	0.44	0.51	
3	3.2	0.51	0.56	
4	31.0	0.51	0.58	
5	29.0	0.45	0.51	
7	27.0	0.55	0.59	
8	18.0	0.51	0.56	
July 15	20.0	0.48	0.52	
25	33.0	0.35	0.41	
Aug 22	37.0	0.41	0.49	
Aug 22	37.0	0.41	0.49	
8	29.5	0.43	0.48	
10	22.5	0.40	0.45	
12	28.0	0.38	0.42	
15	27.0	0.41	0.45	

* The dog was operated on December 3 to increase the severity of the stenosis. A silver band was placed about the pylorus after removal of the adhesions. The dog died on December 7. The size of the outlet was 8.6 mm. A duodenal ulcer had ruptured into the liver, with a resulting abscess of the liver. If hypertrophy of the stomach was present, it was insufficient to attract our attention.

The results are for the three hour period after the meal.

seven and one-half months. Gastric tetany was observed in two of the five dogs that died shortly after the production of the stenosis.

In dog 2 (table 1) a decrease in secretion occurred for ten days after the stenosis was produced, following this period, an increase occurred. The acidity of the secretion was slightly increased, the average total acidity for the control period being 0.46 per cent and for the period of hypernormal secretion, 0.49 per cent. This, we believe, is not a significant increase.

In dog 3 (table 2) a decrease in secretion occurred for seven days after the stenosis was produced, following this period, the amount of secretion returned to normal. In two instances the secretion was slightly

above normal, but the increase was not enough to be significant. The total acidity of the secretion did not show a significant change.

In dog 5 (table 3) a marked hypernormal secretion occurred after the stenosis was produced. The copious secretion made it impossible to prevent digestion of the skin about the pouch.

In dog 6 (table 4) a decrease in secretion occurred for three days after the production of the stenosis, after this period, the secretion was definitely increased above normal. An increase in the acidity of the secretion did not occur.

TABLE 2—*Effect of Pyloric Stenosis on Gastric Secretion*
Dog 3* with a Pawlow pouch

Procedure	Amount in Cc	Free Acidity	Total Acidity	Comment
Control Period before Stenosis				
May 18	18.3	0.48	0.53	
19	27.0	0.47	0.53	
20	28.0	0.46	0.52	
21	14.5	0.43	0.48	
22	20.0	0.54	0.63	
23	17.5	0.41	0.47	
24	10.0	0.52	0.61	
25	11.0	0.47	0.52	
Pyloric stenosis made with tape, May 27				
May 28-June 1				
June 1	1.0	0.29	0.36	Vomiting
3	3.2	0.51	0.55	
4	9.0	0.45	0.51	
5	21.0	0.45	0.51	
6	15.0	0.52	0.59	
8	18.0	0.51	0.58	
14	12.4	0.42	0.49	Continuous secretion varied, some days normal, others three and four times normal
15	21.0	0.43	0.58	
July 26	14.0	0.42	0.52	
Aug 22	11.0	0.10	0.23	
Nov 4	11.0	0.21	0.30	
7	34.0	0.43	0.50	
8	20.0	0.42	0.47	
9	33.0	0.41	0.46	
11	28.0	0.41	0.45	
13	24.0	0.40	0.45	
15	21.0	0.36	0.41	

* On November 24, the dog was operated on to increase the severity of the stenosis. A silver band in the form of a circle was placed about the pyloric sphincter after removal of the adhesions. The animal vomited intermittently, and died of distemper on December 7. Roentgen ray examination revealed a high grade stenosis. Marked hypertrophy of the stomach was not present. The size of the outlet was 8.5 mm.

The results are for the three hour period after the meal.

In dog 7 (table 5) a decrease in the secretion occurred for one week following the making of the stenosis. During the following two months, the secretion remained slightly hypernormal. The secretion was not studied during the fourth and fifth months. During the sixth month following the stenosis, a definite hypernormal secretion occurred. The total acidity of the secretion was not significantly affected.

Dogs 11 and 12 (tables 6 and 7) possessed a refractory pouch, as is demonstrated by the fact that relatively small amounts of their secretion were of low acidity. In both these animals the amount of secretion shown in the tables represents a ten hour collection after the meal. In dog 11, following the stenosis, there was no definite change in the

TABLE 3—*Effect of Pyloric Stenosis on Gastric Secretion*

Dog 5* with a Pawlow pouch

Procedure	Amount in Cc	Free Acidity	Total Acidity	Comment
Control Period				
May 26	22 0	0 56	0 60	
27	15 0	0 40	0 51	
28	15 0	0 40	0 51	
29	18 0	0 45	0 54	
31	27 0	0 54	0 63	
June 3	25 0	0 50	0 61	
4	32 0	0 47	0 63	
Pyloric stenosis made with silver band, June 6				
June 7	13 0	0 43	0 54	
8	16 0	0 45	0 54	
14	33 0	0 60	0 68	
15	54 0	0 45	0 63	Continuous secretion increased by three times normal

* The dog was chloroformed and death occurred on June 22 Digestion about pouch due to copious secretion made it impossible to obtain accurate figures The size of the outlet was 12 mm

The results are for a three hour period after the meal

TABLE 4—*Effect of Pyloric Stenosis on Gastric Secretion*

Dog 6* with a Pawlow pouch

Procedure	Amount in Cc	Free Acidity	Total Acidity	Comment
Control Period				
May 19	13	0 46	0 54	
20	20	0 46	0 53	
21	22	0 43	0 51	
22	20	0 43	0 52	
23	14	0 43	0 50	
24	19 5	0 46	0 54	
Stenosis made with tape May 25				
May 27	9	0 30	0 37	
28	9	0 46	0 51	
29	19	0 48	0 55	
31	28	0 49	0 61	
June 2	24	0 45	0 54	
3	25	0 54	0 58	
4	40	0 49	0 59	Continuous secretion normal
8	30	0 46	0 51	
15	27	0 45	0 57	
July 25	25	0 49	0 52	
Aug 22	22	0 46	0 52	
Nov 4	27	0 38	0 42	
6	28	0 45	0 53	
8	39	0 46	0 51	Emptying time test showed retention
9	35	0 47	0 51	
12	25	0 44	0 49	
Stenosis made more severe with silver band, stomach was extremely large, a stormy convalescence resulted up to December 15				
Dec 15	15	0 33	0 44	
19				
30	14	0 30	0 45	Vomited meal
31	39	0 45	0 56	
Jan 6	28	0 44	0 49	High continuous secretion
10	30	0 36	0 41	
15	28	0 50	0 52	Emptying time test showed high grade retention

* The dog was chloroformed The size of the outlet was 7.5 mm in diameter The stomach was markedly hypertrophied, but not as much as in dog 7 Its length was 19.5 cm and its width was 14 cm

The results are for a three hour period after the meal

TABLE 5—*Effect of Pyloric Stenosis on Gastric Secretion*
Dog 7* with a Pawlow pouch

Procedure	Amount in Cc	Free Acidity	Total Acidity	Comment
Control Period				
May 27	15.5	0.35	0.45	
28	27.0	0.45	0.51	
29	36.0	0.51	0.55	
31	30.0	0.52	0.63	
June 2	35.0	0.47	0.56	
3	18.0	0.38	0.50	
4	36.0	0.51	0.56	
Pyloric stenosis made with tape, June 6				
June 6	2.0			Mucus
7	5.0	0	0.14	
July 14	22.0	0.50	0.58	
15	14.0	0.45	0.58	
25	21.0	0.33	0.41	
Aug 22	20.0	0.27	0.36	
Nov 6	38.0	0.42	0.50	
7	43.0	0.44	0.52	
8	33.0	0.46	0.51	Continuous secretion is increased from three to five times
9	52.0	0.46	0.51	
10	55.0	0.45	0.50	
11	48.0	0.41	0.47	
12	38.0	0.41	0.46	
13	37.0	0.41	0.48	

* Stenosis was produced with a silver band on December 4. The stomach was extremely large. A stormy period followed and continued until January 24, when the animal was chloroformed. The dog frequently vomited food eaten twenty-four hours before. Accurate tests could not be obtained because of vomiting. January 10 the following data were obtained: the free acidity for 17 cc of gastric secretion was 0.11, the total acidity was 0.20. Little secretion occurred from tests on other dates. Several twenty-four hour collections were made, the greatest amount of secretion collected from these tests being 26 cc. Frequently nothing but mucus was collected. The animal was chloroformed, and autopsy performed on January 24 showed a markedly hypertrophied and dilated stomach. Its length was 26 cm, and its width was 20 cm. The size of the pyloric outlet was 4 mm.

The results are for a three hour period after a meal.

TABLE 6—*Effect of Pyloric Stenosis on Gastric Secretion*
Dog 11* with a Pawlow pouch Ten Hour Secretion

Procedure	Amount in Cc	Free Acidity	Total Acidity	Comment
Control Period				
April 6	21.3	40	60	
8	24.4	45	65	
15	33.1	30	40	Emptying time 4.5 hours
22	25.0	20	32	
May 13	41.3	15	25	
Stenosis made with aluminum band, April 15, a quick recovery resulted				
May 8	20.1	35	47	Emptying time 4.5 hours
Stenosis increased April 29, first meal of meat given on June 5				
June 5	5.7	32	45	Emptying time 6.5 hours
16	20.0	10	25	
23	20.0	25	30	
30	11.4	10	22	
July 7	22.8	15	20	
15	26.7	3	10	Mostly mucus
30	40.4	0	8	
Aug 6	29.2	27	40	
25	22.9	0	8	Mostly mucus
27	12.9	3	10	Emptying time 6 hours, mostly mucus
Nov 3	21.0	0	5	

* The animal was chloroformed on November 15. The stomach was markedly hypertrophied. Acidity is expressed in clinical units.

amount of secretion collected, including mucus, but the actual output of hydrochloric acid was decreased, the secretion after the first month consisting almost entirely of mucus. In dog 12, a decrease in the amount of secretion occurred following the stenosis, but there was no definite change in the acidity of the secretion.

In six of the seven dogs a decrease in the secretion occurred for a few days (from three to ten days after the operation for producing stenosis). Four of the seven dogs (dogs 2, 5, 6 and 7) manifested a hypernormal secretion, one (dog 3) a normal secretion and two (dogs 11 and 12) a hypernormal secretion after the stenosis. Dogs 11 and 12 possibly should not be included, because their pouch was refractory. The acidity of the secretion was not significantly altered.

TABLE 7—*Effect of Pyloric Stenosis on Gastric Secretion*
Dog 12* with Pawlow pouch Ten Hour Secretion

Procedure	Amount in Cc	Free Acidity	Total Acidity	Comment
Control Period				
May 21	21.5	35	50	Emptying time 5.5 hours
28	11.5	35	47	
June 4	13.0	45	55	
5	18.4	53	70	
11	12.0	7	20	
16	7.7	9	22	
Stenosis made with aluminum band, July 2				
July 16	5.4	17	30	Ate part of meal
30	5.1	3	12	
Aug 6	19.6	40	55	Emptying time 6.5 hours
20	6.5	22	37	
25	3.7	20	30	
27	7.9	62	75	
Nov 3	10.1	32	47	

* The animal was chloroformed on November 15. The stomach was markedly hypertrophied. Acidity is expressed in clinical units.

The continuous secretion collected the twenty-third and twenty-fourth hours after the meal was augmented in three of the four dogs (dogs 5, 6 and 7) that showed a hypersecretion. It was augmented in some tests in dog 3, which showed a normal secretion after the stenosis.

Gastric tetany was observed in only two dogs in which the stenosis was marked (dogs 2 and 10).

The stomach was markedly hypertrophied in four dogs (dogs 6, 7, 11 and 12), the greatest hypertrophy occurring in dog 7. That the stomach was hypertrophied and not dilated was shown by the fact that when it was examined, the mucosa of the stomach was not stretched, numerous rugae were present, and the muscularis was of normal thickness (figs 1 and 2).

Because dogs 11 and 12 had a refractory pouch, and because the stenosis did not cause augmentation of the secretion, we determined the acidity of the gastric contents. These observations were made after

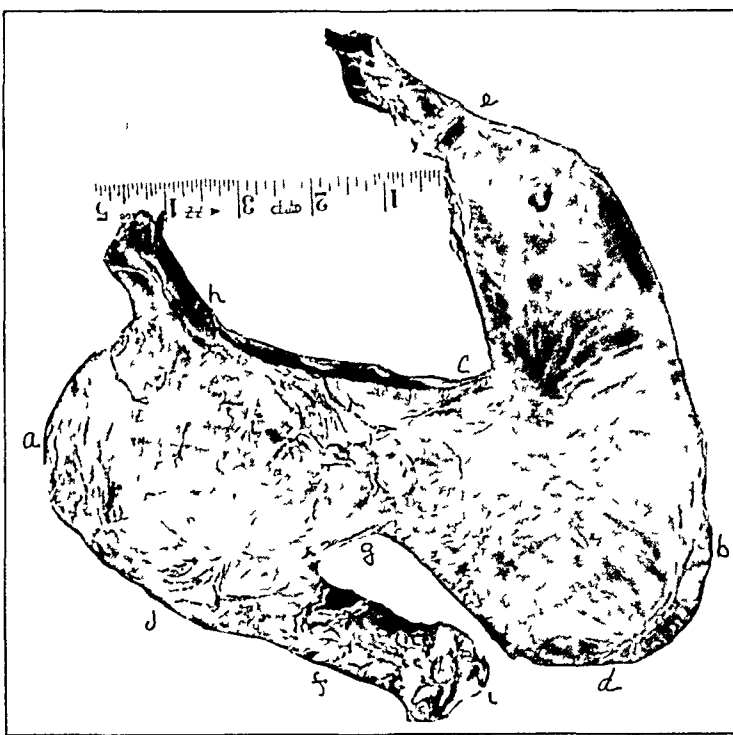


Fig 1—A photograph of the hypertrophied stomach of dog 7 The distance from *a* to *b* measures 26 cm , from *c* to *d*, 13 cm , and from *e* to *d*, 20 cm The esophageal opening of the stomach is indicated by *h*, and the pyloric outlet by *e* (note the band covered with adhesions) The letter *g* indicates the notch in the fundus produced by the Pawlow pouch, *f*, the pouch, *i*, the roset of the pouch The normal size of the stomach of a large dog would be represented by the curvature *a j g c h* Ulcers were not present in the gastric or duodenal mucosa

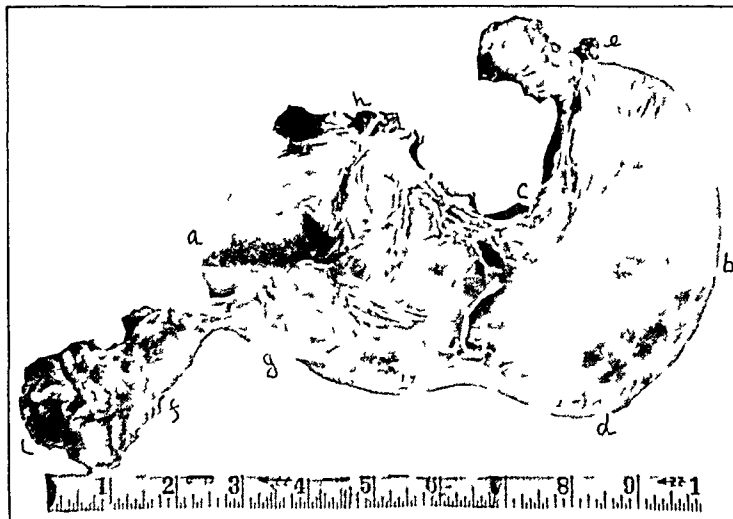


Fig 2—A photograph of the hypertrophied stomach of dog 11 The distance from *a* to *b* measures 22 cm , from *c* to *d*, 9 cm , and from *e* to *d*, 15 cm The esophageal opening is indicated by *h*, the pyloric opening, by *e*, and the pouch, by *f* The refractoriness of this pouch may probably be explained by the contraction of the connective tissue which occurred at the isthmus or at the point where the pouch is connected to the stomach proper In figure 1, it is to be noted that contraction of the connective tissue did not occur

the stenosis was produced. The reason we did not study the acidity of the gastric contents in all our dogs was that we took it for granted, as claimed by Pawlow and his colleagues, that the pouch correctly reflected the secretion of the stomach as a whole, and that at the time these

TABLE 8—*Showing That the Pouch Does Not Always Reflect the Secretion of the Stomach, Neither Acidity Nor Quantity is Reflected*

Dog 11* with a Pawlow pouch, August 27

Procedure	Secretion of Pouch			Gastric Analysis		Time, Hour
	Amount in Cc	Free Acidity	Total Acidity	Free Acidity	Total Acidity	
Continuous meal	20	0	3	0	3	11-12
	07	0	15			12-1
	12	0	38	0	53	1-2
	20	20	45			2-3
	06	5	40	0	68	3-4
	05	0	18			4-5
	08	0	3	15	110	5-6
	30	0	3			6-7
	07	0	3	28	110	7-8
	16	0	3	30	118	8-9
	18	0	3	45	158	9-10
	17	0	3			10-11
	18	0	3	35	105	11-12
	13	0	3			12-1
	19	0	3	20	95	1-2
	16	0	3			2-3
	15	0	3	25	88	3-4
	17	0	3			4-5

* Acidity is expressed in clinical units. This is the type of Pawlow pouch preparation that is known in the laboratory as a "poor secretee" and is usually discarded in most studies on gastric secretion. It is used in this study because the pouch is refractory and would be influenced only by maximal stimuli or procedures.

TABLE 9—*Showing That the Pouch Does Not Always Reflect the Secretion of the Stomach, Acidity is Reflected But Not Quantity*

Dog 12* with a Pawlow pouch, August 27

Procedure	Secretion of Pouch			Gastric Analysis		Time, Hour
	Amount in Cc	Free Acidity	Total Acidity	Free Acidity	Total Acidity	
Continuous meal	05	0	3	0	3	11-12
	02					12-1
	01	0	3	0	40	1-2
	12	0	8			2-3
	07	53	78	0	70	3-4
	10	83	98			4-5
	12	88	100	0	108	5-6
	17	93	103			6-7
	16	90	105	0	133	7-8
	08	113	130			8-9
	05	95	120	0	130	9-10
	05	75	95			10-11
	05	50	85			11-12
	08	38	50	35	103	12-1
	08	35	45	38	100	1-2
	04	30	40			2-3
	08	0	3	40	70	3-4
	14	0	3			4-5
	20	0	3			5-6

* Acidity is expressed in clinical units. This is the type of Pawlow pouch preparation that is known in the laboratory as a "poor secretee" and is usually discarded in most studies on gastric secretion. It is used in this study because the pouch is refractory and would be influenced only by maximal stimuli or procedures.

observations were made we did not realize the importance of mechanical distention as a factor in gastric secretion. The results shown in tables 8 and 9 demonstrate, in a striking way, that the pouch does not always

reflect the secretion of the stomach. We cannot state that the stomach proper in these two dogs showed a hypernormal secretion, because we failed to use controls. The acidity of the secretion in these dogs, however, is not abnormally high.

COMMENT

The temporary decrease in gastric secretion following the production of pyloric stenosis is what might be predicted. Dehydration may have been a factor in some cases.

We believe that the results on four of the seven dogs which survived the stenosis reveal that pyloric stenosis may cause a hypernormal secretion, but not acidity. If one rules out the results in dogs 11 and 12, which possibly should be done because in these cases the pouch was refractory and did not reflect the secretion going on in the stomach, our results would show that four of five showed a hypernormal secretion. This observation on dogs with a Pawlow pouch confirms the conclusion arrived at indirectly by Hamburger and Friedman. It also supports the general impression of clinicians that pyloric obstruction is generally associated with a hypernormal secretion.

We believe that the method used in our experiments for the production of stenosis renders only one explanation for the hypernormal secretion possible, namely, that the stenosis caused the increased secretion. However, one can imagine disease conditions in man in which a hypersecretion may be due to the increased absorption of secretagogues in association with a functional pyloric obstruction, for example that which occurs in colitis. One of the authors who has made numerous gastric analyses on himself, and who is subject to intermittent attacks of colitis (irritable colon), has observed that during his attacks of colitis there is a gastric retention, hypernormal acidity of a test meal and an increased continuous secretion.

The explanation of the hypernormal secretion caused by pyloric stenosis is obvious. It is known that the gastric phase of gastric secretion is due to two factors—mechanical distention and chemical contact of substances in food.² It is known that hydrolyzed proteins and the products of digestion stimulate gastric secretion from the intestine.³ It is also known that prolonged contact of digested products in the intestine stimulates gastric secretion,⁴ as does acid in the intestine.⁵ From these facts it follows that pyloric obstruction may cause hypernormal secretion as follows: 1. Gastric retention prolongs mechanical distention and chemical contact. 2. The more complete the hydrolysis in the stomach,

3 Ivy and Javois. *Am J Physiol* **71** 583, 591, 604, 1925.

4 Ivy, Lim and McCarthy. *Quart J Exper Physiol* **15** 55, 1925. Ivy and Javois (footnote 3).

5 Ivy and McIlvain. *Am J Physiol* **67** 124, 1923.

the greater is the effect of the chyme in the intestine and the more easily are the hydrolytic products in the chyme digested by the pancreatic juice. As a result the intestinal phase of gastric secretion would be augmented. 3 As the chyme is more acid, more acid stimulation of gastric secretion would result and more pancreatic juice would be secreted. 4 The slow ejection of chyme from the stomach would prolong the contact in the intestine. The results of our experiments seem to indicate that the gastric factors are more important than the intestinal factors in causing hypernormal secretion. Another possible factor must be considered, namely, that the stenosis increases the irritability of the local secretory mechanism in the stomach. The hypernormal continuous or interdigestive secretion might be explained either by more prolonged contact in the intestine or by more complete digestion due to more complete hydrolysis in the stomach.

The failure to observe a "hyperacidity" in our experiments confirms the prevalent view held by some physiologists and by some clinicians.⁶

The appearance of "gastric tetany" in two of the animals in which the stenosis was severe was to be expected from the observations of Hamburger and Friedman¹ and others.

The hypertrophy and dilatation of the stomach that we have observed in our animals was also observed by Hamburger and Friedman, who found it two months after the stenosis. The hypertrophy in our animals was especially striking.

The failure of the Pawlow pouch always to reflect the secretory activity of the stomach should be especially emphasized. We have suspected this while working on other problems of gastric secretion, and as a rule have not used a dog with a refractory pouch. Two of these dogs (dogs 11 and 12) were used in these experiments, however, because at the time we were not aware of the importance of the mechanical factor in gastric secretion, and also because we desired to determine whether a hypernormal secretion would occur in "poor secretors," or dogs with refractory pouches. The dictum that the Pawlow pouch in a dog reflects the secretory activity of the stomach cannot be taken for granted as a rule, if for no other reason than that the pouch only partly reflects the mechanical factor. Our results on dogs 11 and 12 show that when one studies the effect of various procedures on gastric secretion, using dogs in which a Pawlow pouch has been made, it must be shown that the pouch at least approximately reflects the secretion of the stomach. This must be done in order to avoid mistakes.

The cause of refractory Pawlow pouches is problematic. One of us (Ivy) explains it as being due to contraction of secondary connective tissue at the isthmus which causes a pressure block of the vagus branches

6 Carlson. *Physiol Rev* 3 1, 1923

going to the pouch, the blood supply not being interfered with to any extent, in other words, the contraction of connective tissue changes the Pawlow pouch into a Heidenhain pouch, which is known to be more satisfactory

SUMMARY

Experimental pyloric obstruction was made in twelve dogs with a Pawlow pouch. Seven of the dogs survived for a period of from three and one-half to seven and one-half months. The stenosis first caused a decrease in gastric secretions, later, four of the seven dogs showed a hypernormal secretion, one a normal secretion and two a decreased gastric secretion. The last two should probably be ruled out because their pouches did not reflect the secretory activity of the stomach. The indirect observation of Hamburger and Friedman is confirmed, namely, that experimental pyloric obstruction causes a hypernormal secretion of gastric juice in some cases. The point is emphasized that before Pawlow pouches are used it should be shown that they reflect the secretory activity of the stomach.

The cause of the hypernormal secretion is discussed.

A marked hypertrophy of the stomach occurred in four of the seven dogs.

THE EFFECTS OF MITRAL AND TRICUSPID INCOMPETENCE ON THE WORK OF THE HEART*

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Previous workers on experimentally induced valvular incompetence in the heart have been almost exclusively occupied with lesions of the mitral valve and their limited aspects, namely, the period of the cycle in which the backflow into the auricle actually occurs, the pressure changes set up in the auricle and ventricle and the factors concerned in the compensation of the defect. Other sides of the problem which are at least as important as those mentioned, have scarcely been considered up to now, such as actual measurement of the output from the heart during the course of a lesion, which is the best criterion of compensation, nor has a contrast of the function with mitral lesions been made with that done in the condition of tricuspid defect. The present communication deals with the results of recent work on these problems and is based on a long series of experiments on dogs, operations having been performed on some 150 animals, with a view of ascertaining the points mentioned. The question is treated as follows:

- 1 The output from the left ventricle with and without a lesion of the mitral valve is measured, in varying conditions of flow, resistance to ejection, metabolism, etc., while a uniform temperature is maintained for a given series of observations.

- 2 The output from the left ventricle with a lesion of the tricuspid valve is measured, under similar circumstances to those stated under the first procedure.

- 3 The significance of certain features of the venous pulse record occurring in the presence of the lesions is considered.

METHOD

The largest number of experiments have been performed with artificial circulation, the defibrinated blood passing through an external system with variable resistance, and then through a spiral tube in a bath for heating to a reservoir for return to the venous and pulmonary side, the whole being a modification of what is called the heart-lung method. A calibrated adjustable tap on the tube from the reservoir gives the rate of inflow, that is, the potential and not necessarily actual inflow, to the superior vena cava and right auricle. The head of pressure in the reservoir may be kept practically constant, when no leak exists in the system, by the addition of a little blood from time to

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time The output was measured by noting the time necessary to fill a cylinder of 100 cc capacity at a point in the system beyond the artificial resistance, an equal amount of blood at the proper temperature being at once added to the reservoir so that the head of pressure never varied to more than the extent of 100 cc, a difference in height which causes a negligible variation of supply This time for 100 cc is given in seconds in the second column of the tables The quantity of blood expelled could thus be compared with that permitted to flow in at the venous tap, and the work could be calculated The tube for the production of the lesions was the same throughout It was passed into the heart through the appendix and pushed into the ventricle The lumen of this tube, 4 mm in diameter, was accurately fitted with a smoothly moving piston, this, on being withdrawn, uncovered a side opening, of similar area to that of the lumen, in that part of the tube which remained in the auricle after the end was pushed down into the ventricle through the auriculoventricular aperture The valve in systole closed round the part of the tube between the side opening and the lower end, so that regurgitation did not occur unless the piston was withdrawn This form of auricular tube has already been described by me¹ (fig 1), a somewhat similar one having been previously described by Wiggers² for the ventricle

The volume of blood regurgitated when the side opening in the auricular portion of tube was free varied with differences of pressures, amount of flow, etc, but it could also be varied to the extent to which the plunger was withdrawn, as the size of the auricular aperture could be altered at will The area of outlet from the heart to the arterial system varied according to the size of the heart, from about 50 to 120 sq mm In some cases a single tube in the innominate artery sufficed, in others two tubes of outlet, one in the innominate and the other in the aorta, were used The sectional area of the venous cannula of the inlet generally was slightly greater than that of outlet when one tube only was used for the latter, distinctly smaller when two tubes were used for outlet The recording manometers employed were of the Piper pattern of which the advantages are well known Special screw adjustments made for me by Boulitte of Paris were fitted to the manometer, so that manipulation was easy after insertion They were inserted into auricles, large veins and the left subclavian artery in different combinations to give two or three records at a time, the optical system being employed for taking the records

The manometers were filled with Ringer's solution and all air was expelled from them before insertion The pressure changes within them

1 Barry, D T J Physiol **58** 362, 1924

2 Wiggers, C J, and Feil, H Heart **9** 149, 1922

were photographed by means of light from small mirrors placed on the rubber membranes. The rubber on the manometers was sometimes changed so that the deflections of the beam across the photographic paper varied in extent, but the instruments were always calibrated and the range of the beam was ascertained for every experiment. In some cases it is sufficient to note differences of pressure by a mercurial manometer placed in the arterial system. Electrocardiograms have been combined with many pulse records to verify the phases of the cycle in which

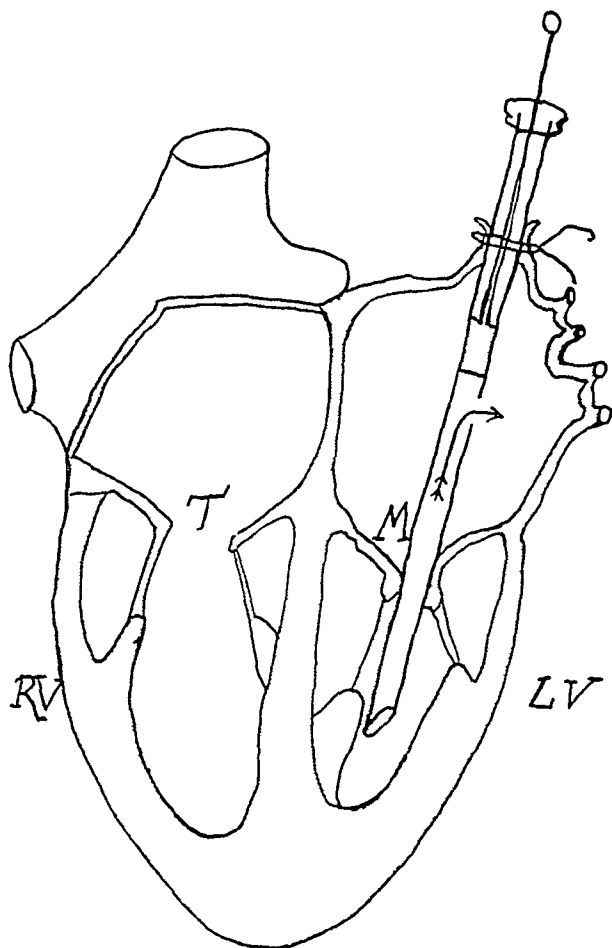


Fig 1—Regurgitation tube in position, and mitral leak occurring to the auricle during ventricular systole

the chief events occurred. Changes in the deflections of the electrocardiogram are caused by valvular defects of the nature of those investigated but they do not form part of the subject of this work.

The arterial side of the apparatus was tested by means of a pressure bottle giving a maximum pressure of 165 mm of mercury. With this head of pressure, fluid was freely driven past an artificial resistance of 100 mm of mercury. Until the difference between the mean arterial pressure and the artificial resistance was reduced to about 20 mm of mercury a fairly steady flow could be maintained through the resistance.

The artificial resistance was set up by air blown into a glass cylinder through which the blood passed in a soft rubber tube. A manometer connected with the cylinder showed the pressure within it. In actual experiment the balance of pressure on the arterial side of the resistance varied in different conditions. The figures for pressures given on the records were obtained from readings of the mercurial manometer taken during the experiment, and from the range given by the optical manometer in calibration.

The heart with natural circulation has been made use of in some experiments after the injection of heparin or peptone to prevent clotting of the blood. Records of the venous pulse have been thus taken with open and closed thorax, but measurements of output have not been made with natural circulation. Direct measurements of the kind done with the artificial circulation are, of course, out of the question for the natural state with ordinary circulation.

For the insertion of the lesion tube and manometers it was necessary to make small openings in the pericardium, but otherwise this membrane was left intact, in some few cases, however, the pericardium was fully opened, and this is specially mentioned when such cases are referred to in the text. The small incisions made in the pericardium to reach the auricular appendixes do not affect its power of supporting the ventricles and preventing undue distention of them. The influence of the pericardium is chiefly felt in preventing overdistention of the ventricles, when it is cut open over the ventricles in the presence of a lesion and high resistance it rapidly swells to such an extent that the muscle fibers are quickly and permanently damaged by stretching. While the closed sac enhances the power to function, its importance in this class of experiment is also evident in the prevention of the injurious effects of severe tests. When, for instance, the sac is opened and an inflow of 1,200 cc per minute is permitted, with an artificial resistance of 130 mm of mercury, a heart weighing 100 Gm becomes much dilated when valvular defect ensues and does not last long, whereas with intact pericardium it carries on fairly well in these conditions, although the full potential flow is not ejected.

The thorax also influences the function of the heart. This is well recognized, and Howell³ even says that investigation of output when the organ is exposed does not give reliable results. That is true for conditions with natural circulation, but it is difficult to imagine how the open thorax could so affect the value of results with the heart-lung method.

The influence exerted by the natural respiratory movements is certainly annulled when the chest is opened, and this hampers action

³ Howell, W. H. Text Book of Physiology, Philadelphia, W. B. Saunders Company, 1927.

when one is working with natural circulation. There are further objections to the method with natural circulation and open chest walls for the present purpose, namely, the difficulty of measurement and control of flow and resistance. But all such objections are overruled with the heart-lung preparation, in which the venous supply is independent of respiratory aids. It may be thought that the artificial inflation of the lungs necessary with the open thorax causes an obstruction to the pulmonary circulation. I have frequently caused free expansion of the lungs without altering the output. Similar observations have also been made by Romm⁴. Accordingly, there is no reasonable objection on such grounds to basing conclusions concerning the function of the heart on observations made in these conditions, and this especially applies in the determination of differences in work caused by lesions, etc., rather than of what a given organ is capable of doing in a general way.

Three chief sets of conditions have been chosen to work with for the preparation. First, the artificial resistance was kept at about 70 mm of mercury, though this was sometimes raised, and the venous flow was not greater than 700 cc a minute. These and lower figures represented best the conditions in which output corresponded with potential inflow when one arterial cannula was used for output. With higher flow and pressure, some discrepancy was noticed between output and supply of blood. In the second series, an aortic cannula for outlet was added to that in the innominate artery. The artificial resistance was kept at 120 mm or lower, and the inflow per minute was from 800 to 1,000 cc. The third group comprised those experiments in which a resistance up to 150 mm of mercury, and a flow reaching to as much as 1,500 cc per minute, were employed. More severe tests than these were not considered of practical utility. The vagi were cut before the artificial circulation was started. Patterson and Starling stated that a heart weighing 56 Gm. can deliver 3,000 cc of blood per minute⁵. My own experience is that in such conditions the heart deteriorates quickly, if valvular defect is occasionally introduced, and that it is not advisable to exceed a flow of 1,800 cc for any length of time when one is dealing with experimental lesions. This aspect of the question will be referred to again. It is necessary to state that the insertion of the lesion tube does not affect the capacity of the organ to function.

The hearts used were large and the weights given seem high. Stripped of the large vessels, pericardium, etc., the organs generally were about 0.6 to 0.8 per cent of the body weight.

4 Romm, I. O. *Arch. f. d. ges. Physiol.* **203** 113, 1924.

5 Patterson, S. W., and Starling, E. H. *J. Physiol.* **48** 357, 1914.

SECTION 1

In the comparison of mitral and tricuspid defects it is essential to bear in mind one important and constant difference between them in the condition of the pulmonary circulation. It has been pointed out that obstruction of the pulmonary circulation accruing from mitral lesions aggravates pulmonary edema and hastens its onset when the state of the blood is favorable to its occurrence. In a right side lesion the aerating surface of the lungs is not affected and the oxygenation of the blood is carried on efficiently whereas the pulmonary congestion resulting from uncompensated mitral trouble soon becomes an effective cause of anoxemia so that apart from the mechanical disability which is greater with mitral interference the loss in aeration intensifies the effect of this latter lesion. This difference has been remarked by Doumer⁶ in the effects of cardiac thrombosis on the right and the left side when the heart muscle is not directly impaired. In chronic lesions one can distinguish between the right and the left side in the preponderance of hepatic or pulmonary symptoms respectively. The point will be considered again in section 2.

The extent to which output is affected by defective closure of the mitral valve depends apart from the magnitude of the defect in itself (size of leak), on three main factors, the degree of resistance on the arterial side, the amount of venous flow and the state of metabolism of the organ. Of course, the weight of the organ used must be taken into account with uniform dimensions of leak. The two first conditions are an expression of the amount of work to be performed, and of these the resistance is the more important, while the third factor is concerned with the state of the muscle which has to effect it. As a general observation it may be stated that with an artificial resistance not exceeding 100 mm of mercury and a venous flow of 1,000 cc, a heart weighing 100 Gm is definitely affected in efficiency by a mitral lesion of the dimensions employed in this work. It is not easily compensated, and though the output rises in the course of four or five abnormal beats it does not reach the quantity ejected prior to the lesion until the leak is closed or the artificial resistance much reduced. The balance of pressure on the arterial side necessary for forcing of the resistance is not recovered otherwise. It is important to note that mere increase of venous flow though it leads to some increase of output is not sufficient to restore the previous output. That the presence of the tube is not the cause of defective compensation is implied in what has already been stated, that the insertion of the tube does not per se diminish output, there is an immediate return of efficiency when the piston is pushed down, as is obvious from the records (figs 2 to 6). The record in figure 2 is that of a heart of

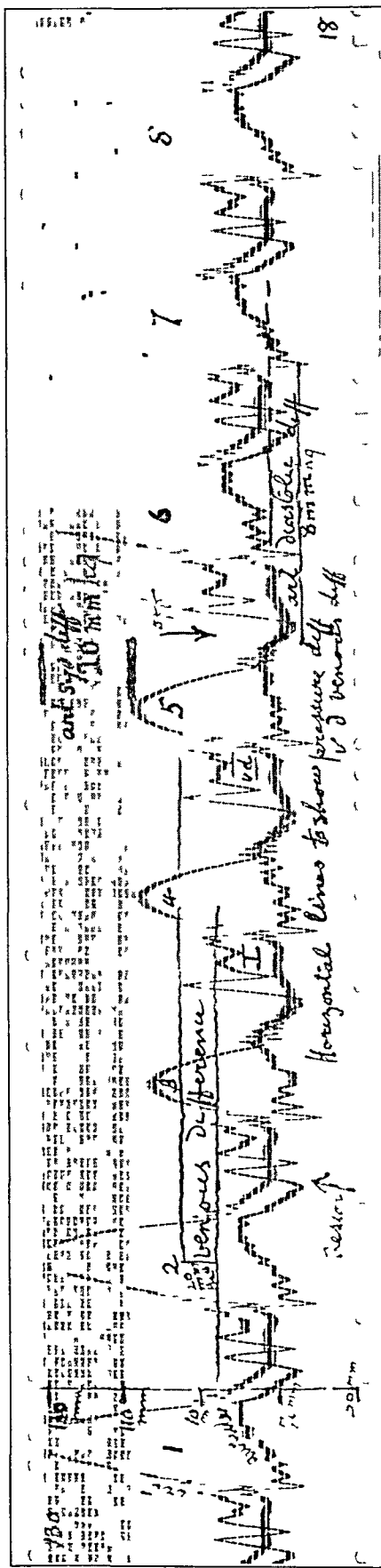


Fig 2—Records from left subclavian artery, and right auricle, mitral regurgitation, systolic arterial pressure—130 mm of mercury, diastolic arterial pressure—75 mm of mercury, lesion at arrow after second cycle, nos 3, 4 and 5 are regurgitant cycles, fall of systolic pressure equal to 24 mm of mercury in cycle 3, fall of systolic pressure equal to 22 mm of mercury in cycle 5, fall of diastolic pressure equal to 8 mm of mercury, instant recovery of arterial pressure when the leak was shut down at inverted arrow after cycle 5, further description is given in text, the time in all records except 1 and 2 is given at the top in tenths and twentieths of a second

115 Gm with a venous flow of 1,000 cc and artificial resistance of 100 mm of mercury. The manometers were inserted into the right auricular appendix and left subclavian artery. The fall of systolic arterial pressure due to lesion is well demonstrated (about 20 to 22 mm of mercury). In a later part of the record, with repetition of the lesion, this lowered pressure was seen not to rise more than from 6 to 8 mm of mercury after half a minute's duration of defect in the valve. The record was taken within a quarter of an hour from the beginning of the artificial circulation, and nearly all the results given were obtained from organs not later than half an hour from this starting point. Experience has shown that a preparation begins to deteriorate after this interval. This is especially true if more than a thinning of tissue is tied off from the auricles when the tube or manometers are inserted. A small portion of this tissue is sufficient to prevent bleeding at the site of the ligature. It has also been noticed that prolonged high resistance to output has a depressing effect. If after a lesion has existed for some time the output and arterial pressure are quickly restored to their former level when the leak is stopped, as happened in several trials with the organ from which figure 3 was taken, it is concluded that the heart has not been affected by the abnormal conditions, and it may be employed for further tests.

It is impossible to state the actual amount of reflux in each case, but it has been calculated to vary from 2 to 7 cc per beat, according to relative pressures in aorta and auricle. The aperture for leak was relatively large compared with the sectional area of the aperture of outlet when this was confined to the innominate artery, because similar relative dimensions must be common in natural defects. Wiggers² has shown that in the heart with natural circulation compensation of a small leak is fairly good.

With regard to the condition of the heart muscle, it can be easily affected by an alteration of the amount of ventilation of the lungs, and this is best done by means of an aperture in the tracheal cannula, the size of which can be varied at will. The opening in the cannula was uncovered for defective aeration. When the supply of air is diminished in the presence of a lesion, the function of the heart usually drops in quantity, the organ fails to eject an amount of blood equal to that previously expelled. When a lesion is not present, the same degree of anoxemia, in otherwise similar conditions, does not cause an equivalent reduction of output. This has been observed frequently when in given circumstances the output was reduced by the setting up of a valvular lesion and was still further diminished when the air supply was cut down. Less than a minute was required to bring about the deficiency of function caused by limiting the expansion of the lungs.

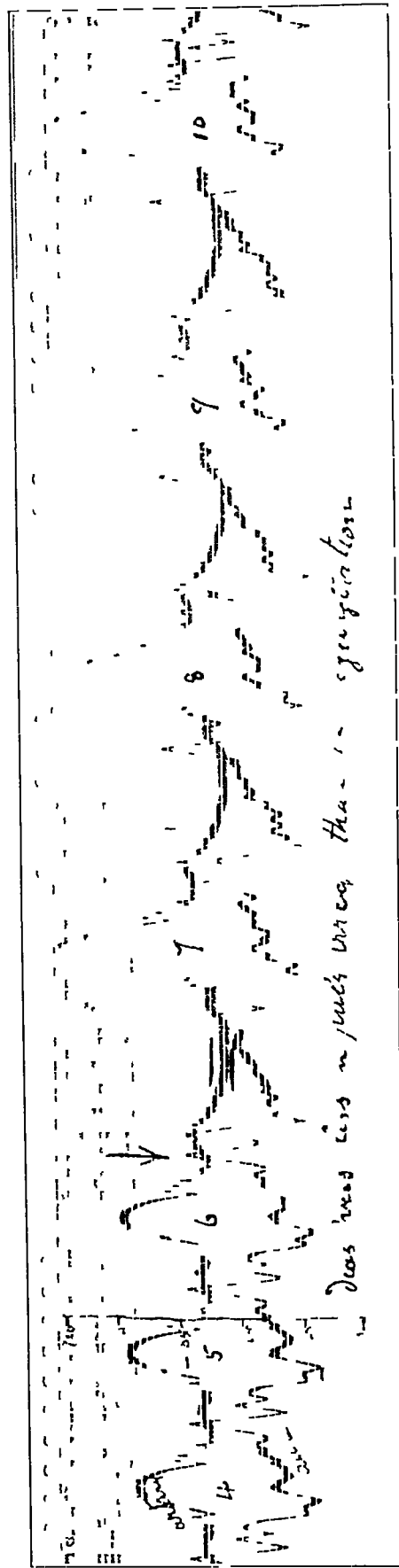


Fig 3—Records from subclavian artery and right auricle, mitral lesion in beats marked 4, 5 and 6, leak stopped at inverted arrow, the succeeding beats show arrhythmia with a rise in auricle pressure

After-effects of lesions are sometimes observed, and they take different forms. A continued diminution of output and failure to recover the initial arterial pressure are of common occurrence. Extrasystoles frequently appear during and after the lesion, and arrhythmia is sometimes established (figs 3 and 4). The record in figure 3 was taken to show the abolition of a lesion which had existed during six cycles. The ensuing abnormal rhythm continued for a period of twenty-one cycles, and the returning normal beat (twenty-second cycle from shutting down the leak at the arrow in figure 3) is shown in figure 4.

The figures in table 1 give some idea of the interference with the circulation caused by mitral leak with constant average ventilation. It shows too that the output is sometimes deficient with respect to supply, but this may be due to slight errors in calibration, even though the latter is effected under uniform conditions of temperature and viscosity of the fluid used.

TABLE 1—*Results with Hearts Weighing 100 Gm*

Minute Volume Inflow, Cc	Time in Seconds for Output of 100 Cc	Minute Volume Output, Cc	Difference, Cc	Rate	Difference per Beat, Cc	Artificial Resistance	Temperature, C	Lesion
500	8	750	50	80	0.625	90	37	0
500	11	545	255	70	3.6	90	37	+
500	8.6	700	100	80	1.25	120	37	0
500	13	461	339	70	4.8	120	37	+

The time of output of 100 cc is given in table 1 for different conditions, and the minute volume calculated from this may be contrasted with that of potential inflow. The absence and presence of lesions are indicated by the signs 0 and + respectively.

The normal state of the heart is not necessarily restored immediately after the defect is remedied, nor is its working power constant at different periods during the influence of the defect, although the conditions of ventilation, pressure, etc., remain the same. Ordinarily, however, it is remarkable to note the consistency of the results. The estimates remain the same in numerous trials for given conditions over long periods, and the time of output is repeated with considerable regularity. It is sometimes difficult to make sure that a lesion is producing its full effect, the intensity of the thrill felt being deceptive according to the direction of the jet. If the opening of the tube within the auricle is too high, the walls of the appendix may be drawn tightly over it and oppose much resistance to the occurrence of a leak. When contradictory or anomalous results are yielded with a lesion, some such cause will generally be found, and it is then necessary to shift the position of the tube or merely to rotate it. One must also avoid pushing the tube too far down into the ventricle. In a small

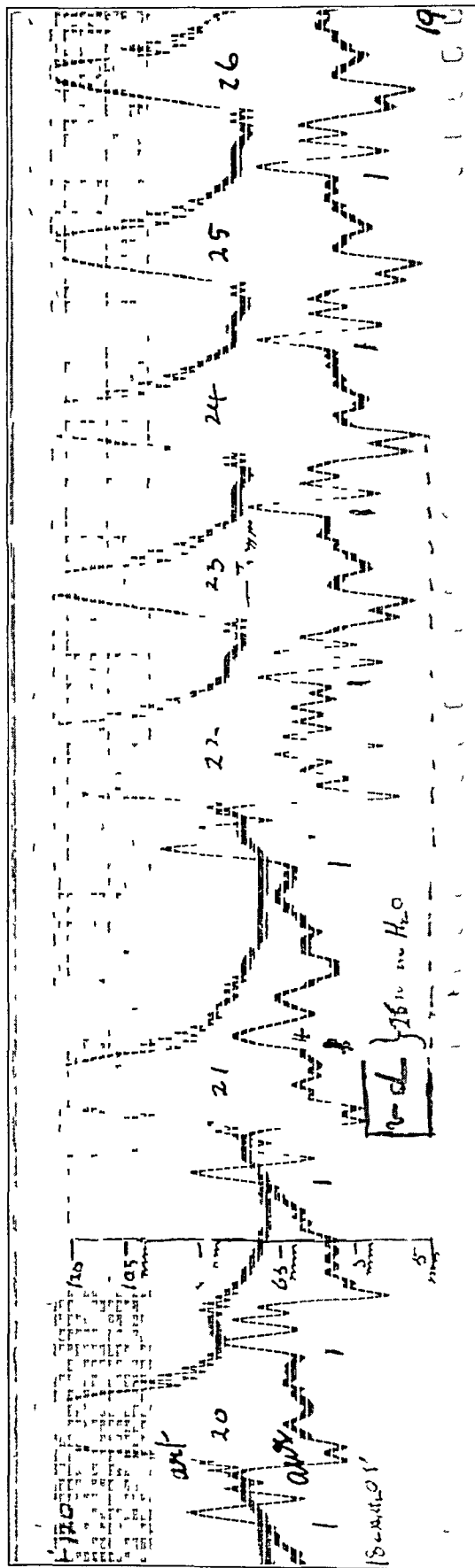


Fig 4—Continuation of figure 3 with cessation of arrhythmism in twenty-second ventricular cycle after mitral lesion, the auricle cycle marked 4 is premature, and this heralds normal rhythm, with marked fall in venous pressure

heart, a second opening on the wall of the tube, a few millimeters from the lower end, obviates the possibility of blocking this end when it touches the ventricular wall. The same tube was used throughout these experiments and was found suitable for every size of heart employed. Once a preparation has been made, the greatest care should be taken to ascertain, by withdrawal of the plunger, that a full leak has been established, then, with manometers properly fixed in position, nothing need be disturbed by the subsequent manipulations and the preparation is reliable.

As showing the regularity with which counts are repeated for the same conditions, an example may be cited from an experiment with a heart weighing 90 Gm. With the inflow tap marking 700 cc and an artificial resistance of 70 mm of mercury the time of output of 100 cc was 8.6 seconds without lesion and 10 seconds with lesion. These times never varied by more than 0.2 second for like conditions in the course of four estimates spread over half an hour, various counts under other conditions having been made in the intervals. Differences become more marked as the work called for increases, according to the size of the heart. With a large heart giving an output of from 15 to 20 cc per beat or more, a lesion caused by the tube used is almost fully compensated after a few cycles, when the artificial resistance is not too high. In an animal weighing 20 Kg the heart weighed 120 Gm. In experiment this heart gave with a flow of 1,300 cc a count of 4.6 seconds without lesion, and 5 seconds with lesion for an output of 100 cc, with an artificial resistance of 100 mm of mercury. That represents, with a rate of 90, a deficit caused by the lesion of little more than 1 cc per beat. When the resistance was increased to 140 mm of mercury, the counts were 6 seconds without and 8 seconds with lesion. The fall in systolic arterial pressure following the lesion was small in the first instance, but it amounted to 15 mm of mercury in the second. As long as the resistance remained at about 100 mm, little diminution of function resulted from the defect. Of course there is a liability to error in counting, but in carefully repeated observations it does not amount to more than \pm or -0.2 second.

The influence of an increase in the peripheral obstruction in its effect on the compensatory reaction of healthy muscle is significant. So far as these artificial conditions indicate, the obstruction is a strong factor in reducing efficiency as measured by the work done with lesion.

The lowering of diastolic arterial pressure resulting from lesion has been considered an aid to ejection. In this connection it is necessary to consider a few points which have presented themselves in the present work. The diastolic fall is shown to vary from a few to about 22 millimeters of mercury in an average case, while the peripheral resistance remains fixed. In the natural vascular system the mean pressure

gradient is fairly uniform at different distances from the heart to the capillaries. In the artificial scheme one can scarcely speak of a pressure gradient between the heart and resistance tube. The obstruction at this latter point is abrupt. When the pressure is lowered on the proximal side of this obstruction, there is greater facility of output into the arterial system, but no reduction of the resistance to onward flow at the tube. A due circulation past this obstruction depends on an ample mean pressure in the arterial system. The lowering of diastolic pressure due to lesion, while it facilitates systolic output, diminishes the available power to force the peripheral obstruction. When the difference between the arterial pressure and the fixed resistance was reduced to about 20 mm. of mercury, the flow to the venous side was greatly diminished, and intermittence occurred. Hence, in the artificial scheme the arterial system is placed between two difficulties, one at the cardiac end demanding a reduced pressure and one at the peripheral end demanding a high pressure. Any increase in this peripheral resis-

TABLE 2—Results with Hearts Weighing 120 Gm

Minute Volume Inflow, Cc	Time in Seconds for Output of 100 Cc	Minute Volume Output, Cc	Difference, Cc	Rate	Difference per Beat, Cc	Artificial Resistance	Temperature, C	Lesion
1,200	5	1,200	—	90	—	120	36	0
1,200	5.4	1,110	90	90	1	120	36	+
1,200	6	1,000	200	90	2.2	140	36	0
1,200	7	857	343	80	4.3	140	36	+
1,200	9	666	534	80	6.6	150	36	+

tance has always a marked effect in increasing the harm caused by lesion. In natural conditions, when the arterioles are rigid, a comparison may be made with the artificial scheme which provides an indication for relief of the obstruction in conditions of the heart. In table 2 will be seen some details of the effects of a lesion in a large heart with the introduction of high resistances and large venous flow. One is led to think that in natural lesions of the valve in man the peripheral resistance in the arterioles, as compared with arterial resistance, that in a finger contrasted to that in the arm, for instance, is an important condition to determine. A high resistance in the arterioles may coexist with a comparatively low mean or diastolic arterial pressure. The pulse pressure is reduced, and the diastolic pressure remains high.

In the cases recorded in table 2 the valvular defect at first caused moderate reduction of the volume of output amounting to about 1 cc per beat. In calculating the work the total resistance was arrived at by adding from 25 to 35 mm. of mercury to the fixed resistance to allow for the excess of mean arterial pressure over this. The actual function has been calculated for most of the observations. For the preparation in table 1 it was estimated as follows. With an output of

750 cc and a rate of 80 (read on the record), the output per beat was 94 cc. This was driven against a total resistance of 115 mm of mercury ($90 + 25$). So with a sectional area of outlet of 50 sq mm, the work per beat was about 1,400 Gm cm or 112,000 Gm cm for a minute's function.

When the lesion set in, the output per beat was $\frac{745}{70} = 7.7$ cc. This was ejected against a resistance of 100 mm of mercury (the mean arterial pressure had fallen about 15 mm of mercury), and the work accordingly amounted to about 1,150 Gm cm per beat, a reduction of 325 Gm cm, or 24,500 Gm cm per minute. The output per beat varied in ordinary conditions from 9 to 20 cc. The change of rate resulting from a defect is slight, as a rule, unless some form of arrhythmia sets in. That mentioned in the foregoing calculation for table 1 was exceptional. In figure 2, for instance, there is practically no change of rate, while in other cases it amounts to a few beats. Curves have been plotted at different intervals after the onset of a lesion to show the relation between output and resistance when the flow, temperature, etc., are constant. They show somewhat irregular form beyond a certain pressure which varies for different preparations.

Even when valvular defects are not present the function of the heart deteriorates with anoxemia, but the deficit is greater and more quickly established when the lesion exists. An increase in the inflation of the lungs in the presence of a lesion will cause a marked improvement in the output when this has been lowered by deflation.

Another condition which should be briefly considered under this section, is that of the heart stripped of its pericardium. The deficiency of compensation, compared with intact condition, becomes apparent only with high resistance. A lesion set up in such conditions causes the heart to become distended and the output to be greatly reduced. The minute volume of output may be reduced by an increase of resistance in the normal condition, when the pericardium is opened, and when the lesion is introduced the effect of increased artificial resistance becomes marked, the function being cut down to small proportions. Apparently, a mitral lesion in certain circumstances causes some disturbance of the heart's efficiency, which is not simply measured by the withdrawal in reflux of a certain quantity of blood from the volume to be ejected. Probably a lowering of coronary pressure affects it. Cardiometer records are not of much use for showing the increase of systolic volume when the pericardium is open, because the distention is to some extent masked by the instrument. Without the pericardium, the leak alone may be less than the measure of failure in output following the lesion. The heart in these cases remains distended in systole out of proportion to the diastolic volume, and its power of contraction

is definitely interfered with, an interference which must be independent of anoxemia, because of its rapid appearance

To conclude this section it is necessary to allude to previous work on the measurement of output from the heart when no lesion existed⁵ For instance, it was said that the maximum of output may be 3 liters for a heart weighing 56 Gm The hearts used in the present experiments were in general much larger than this, it is necessary to employ large organs to produce lesions easily The artificial resistance is not stated in the report mentioned Presumably, the output was effected through two cannulas, in the innominate artery and the aorta, but measurement of the exact amount of inflow is not given As already stated, I was not concerned with these large quantities of blood for output, but it was found that for the output of 2,000 cc per minute, the artificial resistance had to be comparatively low Contrary to what might be expected from the results of the observers here referred to, although they were not concerned with valvular defect, the artificial resistance is an all important factor in aggravating the effects of lesions In the presence of a mitral lesion in practically any circumstances, an increase of the fixed resistance almost invariably leads to a further reduction of output which may be slight but is generally noticeable or considerable

SECTION 2

It has been said by Mackenzie⁷ that tricuspid regurgitation is common in "normal" human beings, and that it may be in part responsible for the formation of the *V* wave in the venous pulse The force exerted in systole of the right ventricle is somewhat less than half that of the left, but the difference of resistance to be overcome corresponds pretty well with this It is important to consider a comparison of the differences prevailing between aortic and left auricular pressures in dealing with tricuspid and mitral lesions, respectively Obviously, the difference favors a much larger jet on the left side than on the right side, if one may judge by comparisons of the corresponding records (fig 5 with fig 6) The same manometer was used for both sets of records, but in different hearts The conditions of pressure, flow, etc, were the same, and the hearts corresponded closely in weight

Near the center of the summit of the reflux wave in the right auricle (tricuspid lesion) are seen two or three large sharp oscillations which correspond in time with the vibration due to the semilunar valves on the arterial curve One of these oscillations marks the beginning of diastole, generally the highest, it is like the pointed elevation described by me⁸ on the *V* wave in man, it marks the highest point of intra-

7 Mackenzie, J Am J Med **134** 12, 1907

8 Barrv D T J Physiol **59** 293, 1924

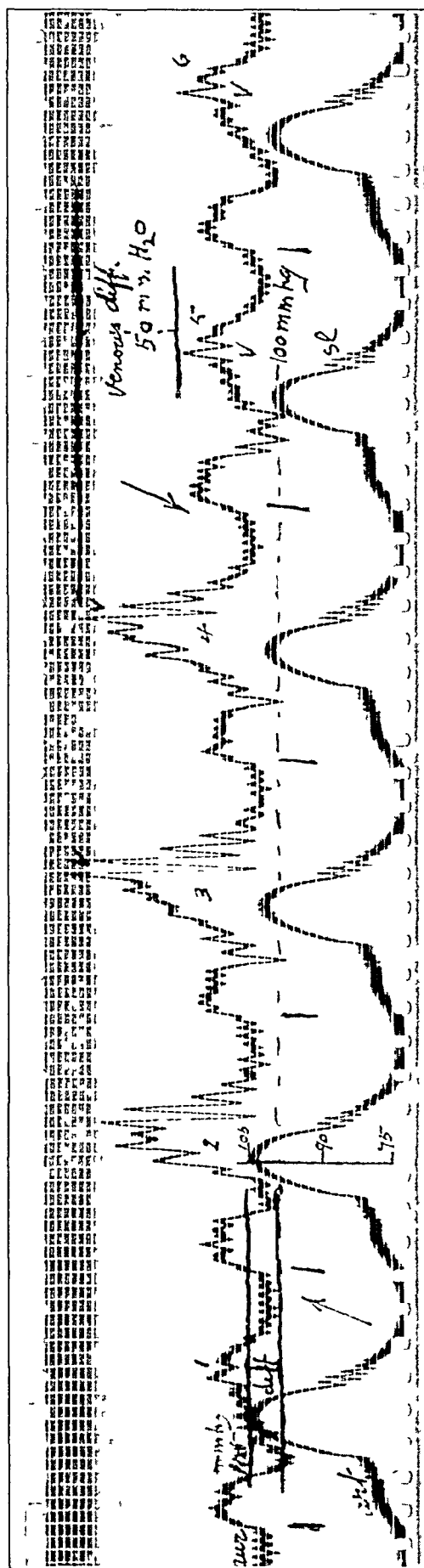


Fig 5—Left subclavian artery and right auricle, tricuspid lesion, well marked effect of reflux in beats 2, 3 and 4, defect produced at upward arrow, and abolished at downward arrow

auricular pressure with tricuspid defect, but not necessarily with normal valve. It is fairly distinct from neighboring oscillations and is seen here even with open thorax, though in the venous pulse generally it is well marked only when the chest is closed. It has, in fact, been ascribed to a possible intrathoracic pressure change, though its causation may be the closure of the semilunar valves. It will be referred to again in section 3 and is mentioned here as marking the summit of the reflux curve.

Regurgitation from the right ventricle has been occasioned by the same tube with a method of introduction through the right auricular appendix similar to that used on the left side. It is evident from the records that output from the left side of the heart is not affected by tricuspid defect in the same way as by mitral defect. The resulting fall of systolic arterial pressure is slight and gradual with the former, measuring no more than from 6 to 8 mm. of mercury in the course of several beats. The returning beat, after the lesion is abolished, usually shows a continued fall, never a rise, of pressure in the arterial system (fig. 5).

The effect of tricuspid incompetence is well marked on the venous side, but the pressure in the right auricle does not rise to a height equivalent to that caused on the left side by mitral trouble, nor does it affect the onward propulsion of the blood to any like extent. The tidal flow after reflux provides a sufficiently large volume for output to keep the pressure in the pulmonary artery nearly up to its former level, and a small increase in inflow is sufficient to restore the arterial pressure (systemic) to its former level. An increase in inflow cannot effect a similar degree of compensation with a mitral lesion, the essential change in the latter condition being a reduction of resistance. Consequently, primary lesions of the tricuspid valve are of less importance than left side lesions from the point of view of function. Increase of artificial resistance has not, in the case of tricuspid leak, any greater effect on arterial flow than such increase produces when no lesion exists, for instance, a preparation in which the heart weighed 100 Gm. was yielding an output of 850 cc. with an inflow of 900 cc., against an artificial resistance of 120 mm. of mercury. A tricuspid lesion was then set up, and the time of output for 100 cc. was 7.4 seconds, the previous time being 7 seconds. On turning the inlet tap to near the mark 1,000, the time for filling the 100 cc. cylinder was reduced to 6.6 seconds, even in the presence of the lesion. Many estimates have been made in this way for comparison with left side lesion effects and all point to the conclusion stated previously.

Defects in pulmonary ventilation, too, have less effect with right than with left side interference. Defective oxygenation affects the muscular work independently of lesion, the ill effects becoming more

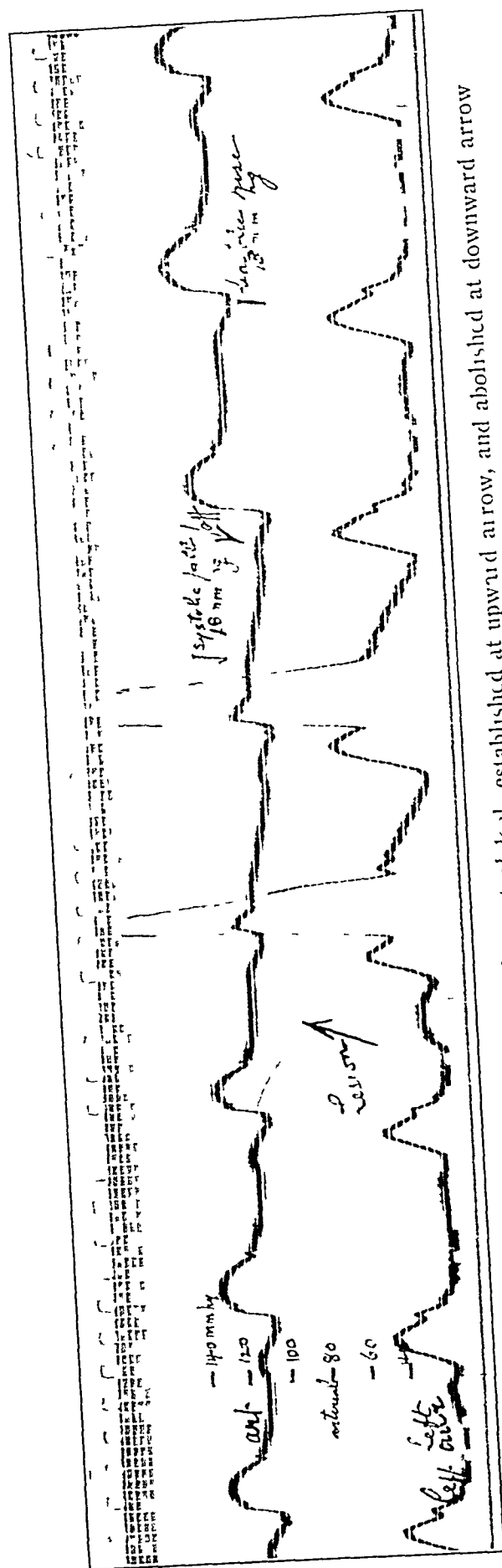


Fig 6—Left subclavian artery and left auricle, initial leak established at upward arrow, and abolished at downward arrow

evident when the lesion occurs, but tricuspid incompetence is not aggravated in the same way by anoxemia as is mitral incompetence. The right ventricle, too, seems to me to resist mechanical interference better than the left, which has gone into fibrillation on many occasions for apparently trivial causes. Because of this tendency of the left ventricle, ventricular manometers, previously used for determining intraventricular changes of pressure, have been abandoned for these experiments and arterial manometers adopted. Even though the ventricles withstand the manometers and seem to act vigorously after their insertion, the functioning power of the heart is not the same as when they are avoided. The pericardium also has to be interfered with for the insertion of ventricular manometers and, as already stated, it is better to preserve it.

Notwithstanding the minor influence of tricuspid leak, it is important to ascertain whether tricuspid insufficiency is, as some observers hold, a frequent sequel to mitral defect or not. The question reappears in section 3, in connection with that of how the venous pulse is affected by left side lesions. Here it is sufficient to state that never in these experiments has a picture presented by the right auricle as a result of mitral defect at all resembled that presented by direct tricuspid leak, experimentally established, as seen in the records (fig 5). Of course, failure to produce this secondary effect of mitral leak lasting from fifteen to twenty minutes at the outside does not connote failure to produce it as a result of mitral defect lasting from fifteen to twenty weeks or months. Yet it is a striking fact that with marked hindrance to outlet on the left side, accumulation in the left side of the heart and pulmonary engorgement, the tricuspid valve remains competent. When the pressure rises in the right ventricle, the systole of this chamber does coincide with a rise in the corresponding phase of the intra-auricular curve, and there may be a small reflux through the valve, but it is not detectable by ordinary means, such as the manometer and palpation for thrill.

SECTION 3

Although the venous pulse record has in recent years become a sort of sheet anchor in the diagnosis of cardiac lesions and the determination of functional capacity of the heart mechanism, it still presents many features, certain oscillations and pressure changes, especially in optical records, the significance of which is by no means understood. A knowledge of these, however, and of the way in which they are affected by cardiac defects is most important for the interpretation of irregular action. It will be best to consider briefly at this stage the various elements constituting the venogram, the three classic waves, *a*, *c* and *v*, with the corresponding dips or depressions. The *a* elevation is generally looked on as being associated with auricular contraction, but the

mechanism of its production, whether by reflux or by rebound from a closed or partially closed venous orifice is not agreed on. Accepting the influence of reflux in its formation—and no one can well doubt it who has observed the filling with auricular systole of the cardiac end of one of the large veins when clamped a few centimeters from the orifice—it is still difficult to say how far the size of a is to be taken as a measure of the force of auricular contraction. In general terms, it may be asserted that with increased pressure in the right auricle, whether caused by augmented inflow or by pulmonary or mitral obstruction, the size of a is increased and its measurement gives some indication of auricular force and intra-auricular pressure. The height of the a summit varies with respiration, being highest after the end of inspiration when intra-thoracic pressure is low and venous inflow is free. This does not apply to conditions with the chest open. Individual peculiarities which give rise to different types of venous pulse are evident only with the closed thorax.

Variations in the size of the a wave and in its position relative to the other elements may occur independently of respiration and of intra-thoracic pressure changes. The question may be supposed to lose in value in light of the view held by some observers, that the auricle is of little consequence as a driving or dynamic factor in the circulatory mechanism—a view which seems to be based on the weakness of the walls of the chamber and on the resistance opposed to the auricular output by the filled or nearly filled ventricle, as well as the facility with which reflux may occur into large veins of low resistance. Feil and Katz⁹ have demonstrated, however, that when the auricles have been made to fibrillate artificially the output is always less than in periods of normal auricular activity. The results certainly point to the possession of dynamic influences by the auricles. It will be shown, presently, that the a wave, or its equivalent in intra-auricular curves, undergoes some increase in size as a result of increased pressure in either auricle.

That part of the auricular record which represents the c wave of the venous record usually consists of two or three vibrations, the first of which corresponds to the c wave proper and precedes the arterial upstroke by one-twentieth of a second. It is of little significance in experimental work beyond showing that an early or presphygmic reflux may occur as indicated by a rise of pressure beginning at this point. The dip succeeding the c elevation in the venous pulse, referred to as the v' depression, generally indicates the lowest point of venous pressure when the chest is closed, and from this point the static rise of venous pressure begins. The position of this dip v' relative to the T deflection of the electrocardiogram seems to me to have some significance as revealing cardiac functional capacity, and it has been dealt with in a

⁹ Feil, H., and Katz. Proc Soc Exper Biol & Med **20** 323, 1923.

previous publication¹⁰ A well marked rise of the point may be observed in the records of tricuspid regurgitation, and this appearance is worthy of attention when such a lesion is suspected The venous pulse has sometimes been taken from the inferior vena cava in these experiments by the insertion of manometers The record then resembles that taken from the auricular appendix, so that the latter gives a picture which may be interpreted in terms of venous pulsation in general

Lastly, the form of the *v* wave may give important information regarding efficiency and type of lesion in a given condition A special oscillation already mentioned occurs near the summit of this wave, which has been described in optical venograms from a man as coinciding with the beginning of diastole before the opening of the auricula-

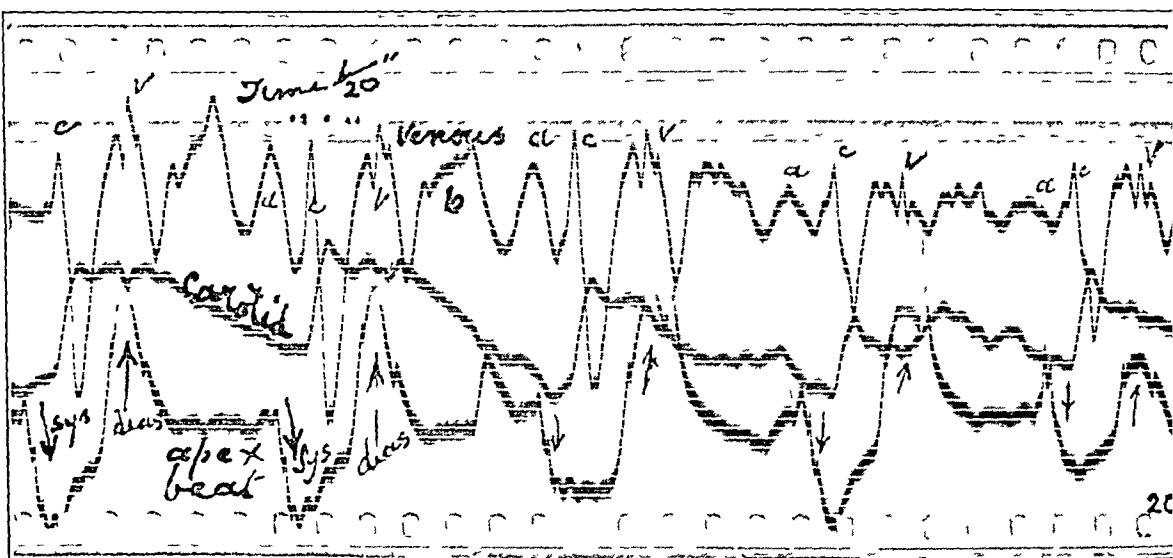


Fig 7—Triple record from normal man, venogram (top), carotid (middle), apex beat (below), this record shows the well marked diastolic stroke against the chest tambour, with sudden rise of intrathoracic pressure after systole, the downward arrow is at the beginning of systole, the upward arrow in diastole, further description is given in the text

ventricular valves An alternative or additional cause of this oscillation to that already mentioned (closure of the semilunar valves) is suggested by records such as that presented in figure 7 This is a triple record venogram (top), carotid (middle) and apex beat (bottom) The apex beat is an inverted cardiogram taken in reality to the right of the apex beat in a young man There is a downward deflection of the beam of light from the mirror on the recording tambour at the onset of systole, that is an expression of the negative pressure in the thorax, accompanying systole (due to the tug of the right ventricle in

¹⁰ Barrv, D T, and O'Donovan, W J Arch int de med exper 2 311, 1926

rotation of the heart) There is a sharp upward deflection at the onset of diastole, that is, an expression of the sudden increase of intrathoracic pressure which marks this phase The apex of this sudden upward deflection corresponds with the sharp oscillation of the *v* wave in the venogram above it, both points corresponding closely with the dicrotic notch of the arterial curve, but it is almost certain that the closure of the semilunar valve which coincides with it could not occasion a deflection of this sort in the curve of the apex beat Systole is marked in the record by a downwardly directed arrow, diastole by an upwardly directed one Consequently there is a sudden sharp increase of intrathoracic pressure at the inception of diastole which can only be yielded by a sudden sharp increase in the volume of the heart Diastole occurs rapidly, if not actively, and is not the gradual process which it is generally considered to be

Patterson and Stirling stated that not only is there no sharp recoil of ventricular muscle with beginning diastole, but also that if blood is not present to distend the fibers, and contractions continue, the volume of the heart will get smaller and smaller But an empty heart suddenly cut out of the thorax of a cat or rabbit, keeps on beating, contracting and expanding, for some time Such curves as that in figure 7 can only be explained by a fairly sharp expansion of the heart chambers It may be that cardiac muscle is slow to return to the relaxed condition after contraction, but it must be remembered that there is a ring or rings, of rigid fibrous tissue in the walls which certainly gives a sharp recoil after compression, a recoil which must cause a sudden change in pressure within the closed space surrounding it

During the influence of the mitral lesion the pressure in the left auricle is high in both systole and diastole, and remains higher than before during at least a few cycles after the lesion The high mean pressure in the left auricle produces some increase of pressure in the right auricle, apparently by direct influence, before there is any effect from pulmonary stasis In the second beat after the mitral lesion the right auricle record shows a change, a rise in level (fig 2), which is intensified and outlasts the lesion when arrhythmia is a sequel (figs 3 and 4) This aspect of the problem has to be developed further before any definite statements are made concerning the particular phases of the venous pulse affected by mitral insufficiency, but the general statement holds, namely, that the venous pulse as indicating right auricle pressure changes does vary in its characters with left auricle pressure changes caused by mitral valvular defect

RESULTS

The methods employed in this work are, of course, open to criticism from different points of view Firstly, there is the condition

of the open thorax, which has been already dealt with to some extent. The normal negative pressure to which the heart is subject in the closed thorax cannot be reproduced in artificial conditions. Efforts to do so have been made in a different form of work,⁵ but when a tube must be introduced into the organ it is impossible. The presence of such a tube is naturally objectionable for investigation, but a better method of producing valvular defect does not suggest itself. From the comparisons of output, before and after introduction, it is obvious that the tube causes even less interference with function than does a manometer in the ventricle. Generally speaking better conditions are not available for the investigation than those chosen and every effort has been made to imitate natural conditions.

Although some discrepancies for the measurement of output in the results of mitral lesion were observed, there was, on the whole, a remarkable uniformity in the estimations for similar conditions, which inspires a certain amount of confidence in applying the results to natural conditions. The function of the heart, when hampered by a defective mitral valve, has been shown to be decidedly diminished in most circumstances. This is aggravated by an increase in the amount of venous inflow. Function decreased to a much greater extent in the case of a mitral lesion than in the case of a tricuspid lesion, in otherwise similar circumstances. Increase of arterial resistance does not add to the deficiency resulting from tricuspid defect proportionately to the depressing influence of rising resistance in the case of mitral defect. An increase of venous inflow does cause an immediate improvement in the function under the influence of tricuspid defect. The effect produced in the pulmonary circulation by failure of the mitral valve adds considerably to the gravity of the condition, because with this there is reduction of aeration of the blood, and this has been shown to cause a marked deterioration of muscular efficiency. The influence of this factor is not so obvious in right side lesions.

Compensation of a valvular defect is supposed to be brought about by the mechanism which enables the heart to yield increased work in physiologic conditions. This view has been put forward by Starling and others¹¹. When the ventricle dilates, owing to a greater volume of blood within it, the stretching of the fibers causes enhanced contractions. But it is necessary to bear in mind the state of the muscle, the energy behind the stroke, so to speak. Hypertrophy provides for this increased demand, hypertrophy with good metabolism. There are limitations to this so-called law of the heart in directing compensation. We have seen what happens under strain when the pericardium is removed, not only, then, is undue distention not responded to by

11 Starling, E. H. *Presse med* 60 29 (July) 1922

enhanced contraction, but also the stretching is a cause of inefficient contraction, and this occurs at a stage before the limits of elasticity or extensibility are passed, as is shown by recovery of contractile power and efficiency in many organs when favorable conditions are restored, after tests in which there was practically no function and the distention of the chambers was great. It was surprising to note the effect of leak into the auricle when a heart without pericardium was acting with large flow against high resistance. The lesion proved to be the last straw which turned the scale, and not only during, but after, lesion the heart refused to function anything like equivalent to the prelesion standard, not at least until resistance to output was reduced.

In disease in man the onset of defects is slow, and in many ways not comparable to the conditions caused in experiment, but in man exacerbations occur, sudden strain, etc., to which the lessons taught by experiment may be applied, and these lessons indicate, above all attention to the peripheral resistance and to the aeration of the blood.

The view put forward by Whitney¹² that the factor of most importance in anoxemia is that of the circulation, those of the respiratory exchange and the blood composition being of secondary consequence, has been opposed by Schneider and Truesdell¹³. The objection is that the respiratory and blood influence is permanent. It is clear from the present experiments that the force and work of the heart is quickly affected in anoxemia. Valvular incompetence is certainly a suitable condition for a demonstration of this effect. Anoxemia produces its effect on the musculature, its influence being apparent, especially with valvular lesions, and the figures given for the changes wrought leave little doubt of the disturbance.

The influence of mitral regurgitation on right intra-auricular pressure curves, though not pronounced, is distinct. It is always revealed by the second regurgitant beat as a rise in general level. The auricular systolic wave rises appreciably higher than in the nonlesion beats, and the succeeding oscillations, synchronous with early ventricular systole, are also raised to a higher level (figs 2, 3 and 4). Obviously, the right auricle was somewhat encumbered by the abnormal phase, and it was suddenly relieved when this ceased.

CONCLUSIONS

The work of the heart when hampered by a defective mitral valve is distinctly diminished in most circumstances. This deficit is made more evident when the venous inflow is increased, and it is decidedly aggravated by increases of peripheral resistance.

12 Whitney, J. L. *Aviation*, J. A. M. A. **71** 1390 (Oct. 26) 1918.

13 Schneider, E. C., and Truesdell, D. *Am. J. Physiol.* **71** 90, 1924.

The results of changing the artificial resistance suggest the importance of noting the degree of rigidity and obstruction in arterioles as compared with mean arterial pressure in man, and ascertaining the pressure gradient

The defect in aeration of the blood occurring with mitral lesion has a deleterious action on the cardiac muscle, and when anoxemia is set up by defective pulmonary ventilation the deficiency in compensation of a mitral lesion is marked

In lesions of the tricuspid valve the influence of a rise in arterial resistance is slight, that of anoxemia is not at all comparable with its effect in mitral incompetence

The fall in arterial pressure with tricuspid lesions is small and of slow onset, that with mitral lesions is marked and of rapid onset

Tricuspid deficiency does not occur in experiment as a result of a mitral lesion

Tricuspid incompetence causes well-marked changes in the records of the right auricle, with a rise of pressure and characteristic vibrations

Mitral incompetence causes changes in the records of the right auricle which are less characteristic than those on right side lesion. Further investigation of these changes is necessary, and there is not any immediate prospect of my being in a position to make it

DISEASES OF THE LIVER

VII FURTHER STUDIES IN EXPERIMENTAL OBSTRUCTIVE JAUNDICE *

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AND

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ROCHISTER, MINN

In a previous paper we have reported the effect of experimental obstructive jaundice on hepatic function as measured by certain tests ¹ At that time particular attention was paid to the changes in the fructose tolerance, the nitrogen partition in the blood, the serum bilirubin and the phenoltetrachlorophthalein test ² We now wish to report further studies with particular reference to the bromsulphalein test of Rosenthal and White,³ the bile acid content of the blood and the elimination of intravenously injected bile acids The serum bilirubin was followed as an index to the degree of jaundice, a standard of reference being thus furnished for the comparison of the results in the two series of experiments

Two groups comprising a total of fifteen animals were studied those in which the common duct had been ligated and those in which cholecystectomy had been performed in addition to ligation of the common duct In all cases complete studies with regard to the tests to be employed were made before the operation and at intervals of from one to three days during the period following obstruction Cholecystenterostomy to relieve the obstruction was successfully performed in two instances and the course of recovery studied

* From the Division of Medicine, Mayo Clinic and The Mayo Foundation

* The data presented in this paper are taken from a thesis submitted by A M Snell to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of M S in Medicine, reported in part before the annual meeting of the American Society for Clinical Investigation, Atlantic City, 1926

1 Snell, A M , Greene, C H , and Rowntree, L G Diseases of the Liver II A Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice, Arch Int Med **36** 273 (Aug) 1925 Greene, C H , Aldrich, Martha, and Snell, A M Studies in Obstructive Jaundice, J Clin Investigation **2** 604, 1926

2 Greene, C H , Snell, A M , and Walters, Waltman Diseases of the Liver I A Survey of Tests for Hepatic Function, Arch Int Med **36** 248 (Aug) 1925

3 Rosenthal, S M Clinical Application of the Bromsulphalein Test for Hepatic Function, J A M A **84** 1112 (April 11) 1925 Rosenthal S M , and White, E C Studies in Hepatic Function VI A The Pharmacological Behavior of Certain Phthalein Dyes B The Value of Selected Phthalein Compounds in the Estimation of Hepatic Function, J Pharmacol & Exper Therap **24** 265, 1924

The animals were kept on a constant diet of meat, milk and dog biscuit. Following the production of obstruction, the changes in the general condition of the animals were essentially identical with those reported in the preceding paper. Anorexia, weakness and progressive loss of weight were constant. To combat this, certain animals were fed daily by stomach tube with a mixture of corn syrup and milk. This served to prevent the immediate postoperative loss in weight, and the dogs remained in better condition than when allowed to eat at will. These animals remained alive and in good condition for a much longer time than those in the first series of experiments. Two survived for periods of 108 and 120 days, respectively, and in these it was possible to study the late effects of complete biliary obstruction.

ILLUSTRATIVE PROTOCOLS

The functional disturbances observed following the production of obstruction to the bile passages were strikingly uniform in both series of experiments. Complete studies were made on animals with obstructive jaundice both in the presence and in the absence of the gallbladder. The four protocols which follow are characteristic of the fifteen animals studied. The changes in an additional experiment are given in tabular form only.

Experiment 1—The dog was an adult female, black and brindle mongrel in good condition, weighing 10 Kg. On Oct 21, 1925, a complete series of functional tests was made, on October 29, under ether anesthesia and with aseptic technic cholecystectomy was performed and the common duct doubly ligated and severed between clamps. The following day the sclerotics and mucous membranes were subicteric, and there was bile in the urine, the functional studies were repeated. On November 1, jaundice was marked, and the stools were light colored. The animal had recovered from the immediate effects of operation and was in good condition. The functional studies are shown in table 1 and in figure 1. This animal was tube-fed on corn syrup and milk, and remained in fairly good condition. The icterus gradually decreased in intensity, and the animal lost weight slowly. After about eight weeks, evidences of collateral circulation appeared on the abdominal wall, and there was also definite distention of the abdomen. On January 1, ascites could be demonstrated, this increased rapidly, and in consequence the weight of the animal showed a marked rise. Figure 2 shows the extent of the collateral circulation in this animal. On February 1, the weight was 11.6 Kg., there was marked edema of the abdominal wall and hind legs. This edema increased progressively up to the time of death, which occurred on Feb 14, one hundred and eight days after the operation.

At necropsy there was marked edema of the abdominal wall and hind legs, 3,800 cc of ascitic fluid was removed from the abdominal cavity. Collateral circulation was well developed, particularly in the vessels of the omentum, which was adherent to the laparotomy scar. The veins of the lower part of the esophagus, the gastric collateral circulation, the veins of Sappey, the splenic vessels and those of the pelvic plexus were dilated. There was only slight staining of the tissues with bile, and the ascitic fluid contained only small quantities of bilirubin. The liver was small, shrunken, tough and reddish-brown with a finely granular mottled surface. There were adhesions of the duodenum to the fossa of the gallbladder. The common duct was greatly distended, being about 2 cm in diameter, and contained a grayish, mucoid fluid. Obstruction to the duct was complete.

TABLE 1—Changes Observed Following Ligation of the Common Bile Duct and Cholecystectomy (Experiment 1)

Date	Time After Obstruction, Days	Weight, Kg	Hemoglobin, Gm	Nonprotein Nitrogen, Mg, Per Cent	Blood Urea, Mg, Per Cent	Serum Bilirubin, Mg, Per Cent	Van den Bergh Direct Reaction	Bile Acids, Mg, Per Cent	Bromsulphalein Test				
									Dye in Serum, Per Cent				
									5 Minutes	10 minutes	15 Minutes	1 Hour	2 Hours
1925													
10-21	0	10.2		25	22	0.0		6.5	20	18	4	1	0
10-29				Ligation of common bile duct and cholecystectomy									
10-30	1	10.0		40	23	3.0	+	9.7	56	40	32	24	14
10-31	2	10.0		22	22	4.0	+	9.1	40	32	30	18	16
11-2	4	10.0		24	13	7.7	+	13.6	32	28	24	16	8
11-4	6			40	26	8.7	+	24.0	52	48	44	26	14
11-9	11			31	25	7.3	+	17.5	64	48	40	24	16
11-13	15	9.6		22	12	5.5	+	11.5	64	48	48	32	24
11-18	20	9.1		30	15	4.4	+	11.3	60	48	40	32	12
11-24	26		12.5	24	11	4.4	+	13.4	60	52	48	28	20
12-1	33	9.3	12.7	27	14	4.7	+	17.2	64	56	56	26	16
12-8	40		10.9	32	17	4.2	+	12.3	64	56	52	32	24
12-15	47	8.5	11.5	22	7	3.6	+	11.7	60	60	56	36	24
12-21	53	7.9	9.8	28	20	4.0	+	7.4	44	40	32	24	24
12-28*	60	7.8	9.6	30	15	3.4	+	8.3	80	56	40	30	16
1926													
1-4	67	10.3	8.8	23		2.8	+	5.8	44	44	40	30	20
1-12	75	10.4	8.3	30	30	2.2	+	8.9	80	60	56	22	22
1-19	82	10.4	8.9	22	12	2.5	+	9.3	76	40	32	28	24
1-28	91	10.6	8.1		16	2.0	+	5.5	60	40	30	22	40
2-1	95	11.6	6.7	27	21	2.1	+	5.1	40	30	30	24	14
2-8	102	12.2	6.4	21		2.2	+	6.1	76	44	38	30	20

* Ascites present

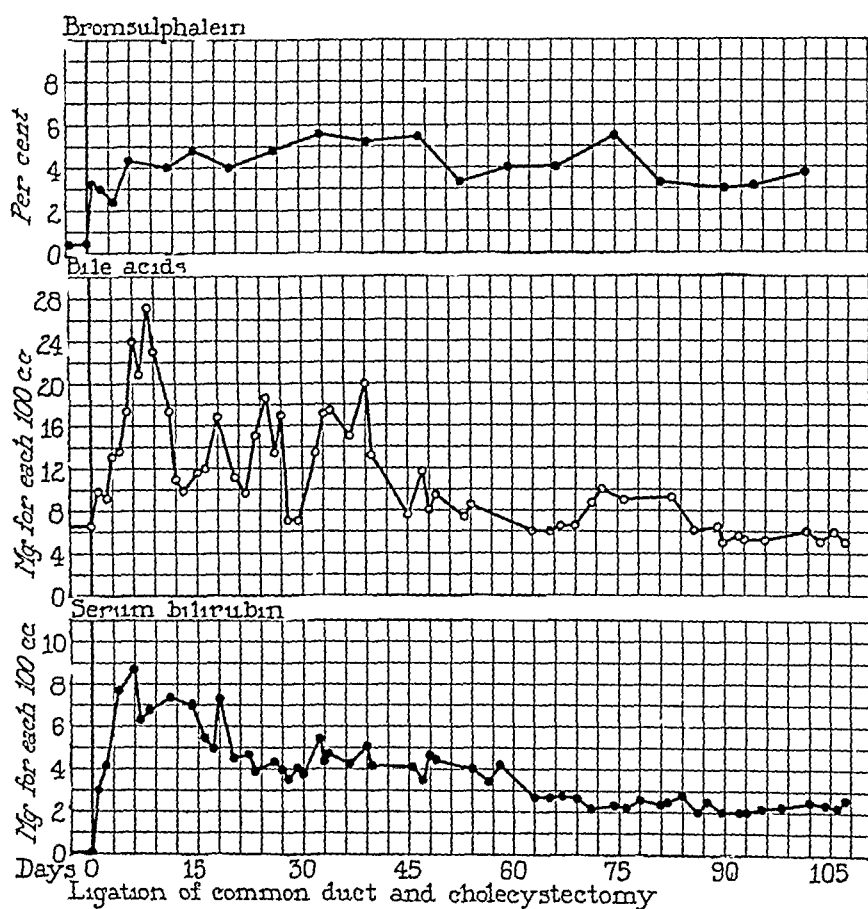


Fig 1 (experiment 1) —Changes in bromsulphalein test, bile acid reading and serum bilirubin following ligation of the common bile duct and removal of the gallbladder

Microscopic examination of the liver showed the presence of chronic cholangitis with thickening of the walls of the bile ducts and infiltration with small lymphocytes. There was fibrosis of the terminal bile ducts and evidence of some regeneration of the ducts. Moderate diffuse infiltration of the parenchyma with lymphocytes was noted. The general appearance was that of monolobular biliary cirrhosis.

Experiment 2—The dog was an adult female mongrel in good condition, weighing 135 Kg. On March 24, 1926, a control series of functional tests was performed. On March 26, under ether anesthesia and with aseptic technic, the common duct was doubly ligated and severed between clamps. The gallbladder was removed at the same time. An increase in the bile salts in the blood was noted one hour later and in the serum bilirubin within four hours. The following

TABLE 2—Changes Observed Following Ligation of the Common Bile Duct and Cholecystectomy (*Experiment 2*)

Date	Time After Obstruction, Days	Weight, Kg	Hemoglobin, Gm	Nonprotein Nitrogen, Mg., Per Cent	Blood Urea, Mg., Per Cent	Serum Bilirubin, Mg., Per Cent	Van den Bergh Direct Reaction	Bile Acids, Mg., Per Cent	Bromsulphalein Test				
									Dye in Serum, Per Cent				
									5 Minutes	10 Minutes	15 Minutes	1 Hour	2 Hours
1926													
3-24	0	13.4	16.4	39	48	0.0	0	6.8	20	8	4	0	0
3-25	0			Ligation of common duct and cholecystectomy									
3-26	1/6	13.1				1.6	+	23.2	36	30	30	22	20
3-27	1	12.6	16.9	30	21	6.1	+	17.4	72	64	56	40	24
3-29	3		15.4	32	17	11.0	+	17.6	80	72	64	40	36
3-31	5		13.5	32	17	23.1	+	33.0	80	72	60	44	24
4-2	7					22.3	+	22.6	90	84	78	52	36
4-5	10		12.0	33	13	16.9	+	11.8	72	66	60	40	24
4-13	18	12.0	15.3	44	50	6.5	+	14.3	56	56	40	32	16
4-19	24	11.9				4.8	+	11.3	64	56	56	44	
4-27*	33		14.3	27	15	2.3	+	6.9	50	40	30		8
5-5	40					1.6	+	6.9	64	64	56	20	8
5-11	41		13.0	28	20	1.6	+	13.7	66	50		16	8
5-18	53	13.3	16.4	33	17	2.5	+	15.8	60	50	32	16	10
6-3†	69	9.4	14.8	22	12	2.4	+	8.8	40	32	32	18	12
6-8	74	9.2	12.8	24	28	3.8	+	9.6		44	40	20	16
6-14	80	10.0	12.3	27	19	2.5	+	12.6	66	66	64	28	18
6-21	87	9.6		27	23	2.0	+	11.4	56	40	40	24	16
6-28	94	8.8	11.4	22	15	1.4	+	13.0	64	40	40	28	18
7-6	102	9.6	11.6	23	11	1.5	+	7.6	80	56	56	32	28
7-9	105	10.3	11.2	24	15	1.4	+	7.8	64	40	40	20	16
7-19	115	12.7	10.0	21	30	1.6	+	10.0	60	60	40	32	20
7-26‡	122	12.6	5.1	23	10	2.0	+	7.9	56	54	50	40	24
7-31	127	11.1	3.7		34		+	4.0	60	60	54	22	

* Ascites present † Paracentesis, 4,000 cc ‡ Paracentesis, 2,000 cc

day the clinical signs of icterus were evident, and the urine contained bile. The animal recovered rapidly from the effect of the operation and remained in good condition, although it lost weight slowly. The changes in the laboratory tests are shown in table 2 and in figure 3. The icterus gradually decreased in intensity although the urine contained bile pigment and the stools remained light colored. Abdominal distention was noted, and on April 27, thirty-three days after the production of obstruction, free fluid was demonstrated in the abdomen. The ascites gradually increased, and on June 3 it was so great as to cause respiratory embarrassment. Paracentesis was performed, and 4 liters (equivalent to nearly a third of the weight of the animal) of bile-stained fluid was removed. The animal remained in fairly good condition for a fortnight, when the abdomen again began to enlarge. At this time the superficial abdominal veins were dilated and there was a widespread collateral circulation. The appetite was

poor, and, although the body weight increased, the dog rapidly lost flesh and strength. On July 26, 2 liters of clear, straw-colored ascitic fluid was removed by paracentesis. Relief was temporary, and the dog died five days later, one hundred and twenty-seven days after the obstruction to the common bile duct.

At necropsy the liver was greatly shrunken, firm and bile-stained. The surface was covered with old organized adhesions, many of which were vascularized. The obstruction to the common duct was complete. It was greatly dilated and filled with a grayish mucoid secretion. The intestines were free from bile pigment. The microscopic appearance of the liver was essentially the same as in the preceding experiment.

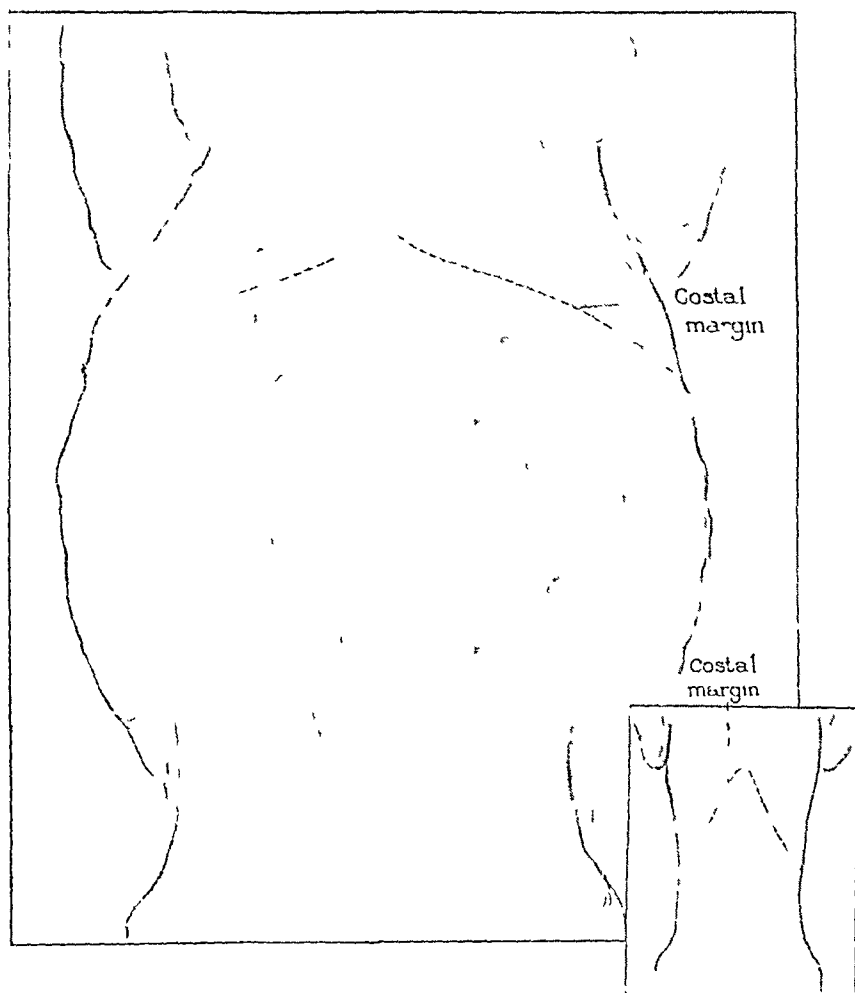


Fig 2 (experiment 1)—Abdominal ascites and extensive collateral circulation in a dog nine weeks after ligation of the common bile duct

Experiment 3—The dog was an adult male, brown and white terrier in good condition, weighing 11.4 Kg. On October 21, 1925, a complete series of functional tests was performed. On October 29, under ether anesthesia and with aseptic technic, the common duct was doubly ligated and severed. The gallbladder was not disturbed. The following day the animal was in good condition without marked postoperative reaction. The functional studies were repeated. On November 1, slight icterus was apparent in the mucous membranes and conjunctiva, the stools were clay colored. The animal was given corn syrup and milk daily by stomach tube, and thereafter remained in good condition with only slight loss of weight. The results of the functional tests are shown in table 3 and in figure 4.

On December 18 an attempt was made to relieve the obstruction. The animal was slightly jaundiced at this time, but careful examination at operation proved that the obstruction was complete. A quantity of thick, black, viscid bile was removed from the gallbladder by means of a trocar, and cholecystoduodenostomy was performed. For the first few days after the operation, the stools were alternately light and dark, but subsequently they uniformly contained bile. The animal remained in good condition thereafter. On January 1, the stools again showed evidence of intermittent obstruction, although the serum bilirubin varied only slightly. The obstruction later became complete, and bile was not apparent in the stools.

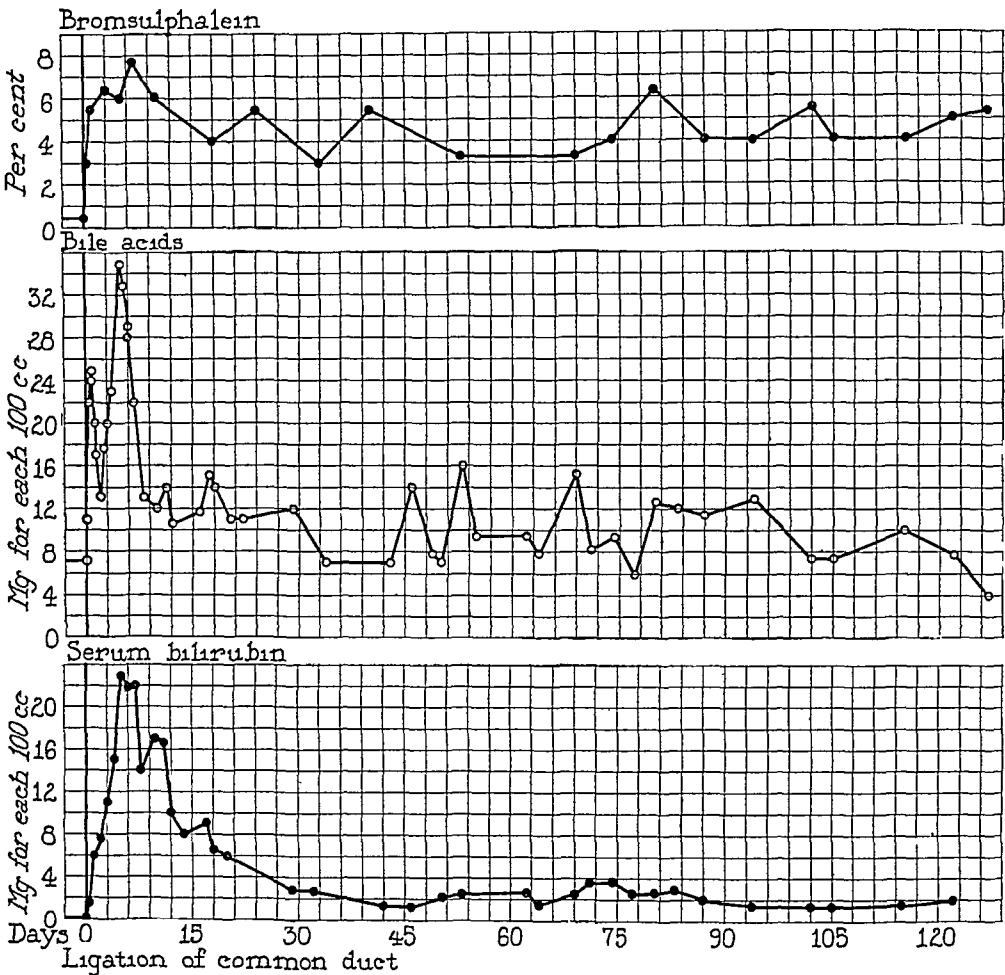


Fig 3 (experiment 2) —Changes in bromsulphalein test, bile acid reading and serum bilirubin following ligation of the common bile duct and removal of the gallbladder

On March 18, the animal was killed, and complete obstruction from post-operative stricture at the site of the anastomosis was found. The liver was small, firm and granular, with definite evidence of biliary cirrhosis.

Experiment 4—The dog was an adult female, mongrel collie, in good condition, weighing 115 Kg. On Jan 6, 1926, a control series of functional tests was performed. On January 14, under ether anesthesia and with aseptic technic, the common duct was doubly ligated and severed between clamps. The gallbladder was not disturbed. Two days later, the animal was in good condition without marked postoperative reaction, the functional studies were

repeated. The serum bilirubin was 0.7 mg, and the next day icterus was apparent in the skin and mucous membranes. The animal was fed dog biscuit and meat with the addition of corn syrup and milk, and remained in good condition without significant loss of weight. The results of functional tests are given in table 4 and in figure 5.

On Feb 16, 1926, under ether anesthesia and with aseptic technic, an attempt was made to relieve the obstruction. A quantity of thick, black, viscid bile was removed from the gallbladder by means of a trocar, and cholecystoduodenostomy was performed. Bile appeared in the stools the following day. Drainage was satisfactory for a short time, but within three weeks the color of the stools

TABLE 3—Changes Observed Following Ligation of the Common Bile Duct (Experiment 3)

Date	Time After Obstruction, Days	Weight, Kg	Hemoglobin, Gm	Nonprotein Nitrogen, Mg, Per Cent	Blood Urea, Mg, Per Cent	Serum Bilirubin, Mg, Per Cent	Van den Bergh Direct Reaction	Bile Acids, Mg, Per Cent	Bromsulphalein Test				
									Dye in Serum, Per Cent				
									5 Minutes	10 Minutes	15 Minutes	1 Hour	2 Hours
1925													
10-21	0	11.4		17	23	0.0	0	6.5	10	4	4	1	0
10-29									16	8	4	0	0
10-30	1	11.4		Ligation of common bile duct									
10-31	2			26	20	0.0	0	6.9	16	8	4	2	0
11-2	4	11.3		36	12	0.0		6.7	20	10	10	8	6
11-4	6			27	17	3.3	+	12.2	22	20	18	16	12
11-9	11			27	15	5.9	+	16.8	56	48	40	24	12
11-13	15	11.1		40	23	5.5	+	23.1	72	56	40	20	16
11-18	20	10.8		26	9	4.6	+	17.2	80	80	56	24	18
11-24	26		11.4	31	15	3.7	+	18.2	56	44	40	20	18
12-1	33	10.6	11.1	35	13	4.2	+	12.7	60	48	44	28	16
12-5	37		11.4	42	11	4.3	+	21.4	64	52	40	24	14
12-8	40			31	18	4.6	+	30.8	64	56	48	28	20
12-9	1	10.5	10.8	Cholecystoduodenostomy									
12-10	2		10.3	30	25	5.3	+	14.2	44	40	32	18	14
12-11	3	10.7	8.7	25	10	4.4	+		54	48	44	24	16
12-12	4		8.6	25	13				64	52	48	28	16
12-15	7	10.8	8.3	28	13	3.6	+	13.6	64	44	40	20	16
12-18	10	10.8		20	9	3.8	+	15.0	80	64	48	32	24
12-21	13	10.5	8.2	12	10	3.5	+	16.0	68	64	40	32	18
12-28	20	10.0	7.1	30	18	3.6	+	19.4	56	48	48	32	24
				36	21	3.2	+		72	56	40	30	16
1926													
1-4	27	10.9	8.8	37	20	2.8	+	25.0	80	48	40	24	20
1-12	35	11.0	9.5	33	22	2.1	+	26.7	60	40	36	20	16
1-19	42	11.2	10.1	21	11	2.6	+	30.6	60	38	30	22	14
1-26	49	11.0	9.3	22	11	3.3	+	8.7	58	38	30	22	16
2-1	55	10.8	10.4	31	19	2.9	+	11.7	60	36	32	28	20
2-8	62	10.7	10.6	30	20	3.8	+	17.5	76	30	30	22	20
2-15	69	10.6	11.5	15	3.7		+	15.5	54	38	30	28	20
2-23	77	10.7	9.7	26	21	2.9	+	13.1	38	30	22	16	14
3-1	83	10.8	11.4	11	4.2		+	15.8	48	44	36	24	16
3-9	91		12.5	11	11	3.8	+	23.8	38	36	32	24	20
3-18	100		9.3	10	13	2.5	+	21.4	38	28	24	24	20

gave evidence of intermittent obstruction, which later became complete. The animal was killed on May 4, seventy-six days after the second operation. The liver was shrunken and contracted, and the gallbladder and bile ducts were dilated and contained a grayish, mucoid fluid. The opening between the gallbladder and the duodenum had closed, and obstruction was complete.

DISCUSSION OF TESTS

Bile Pigments—In our previous paper dealing with experimental obstructive jaundice,¹ particular emphasis was placed on the changes in the serum bilirubin during the first two weeks after the production

of biliary obstruction. Particularly interesting were the differences noted in the two groups of animals with reference to the influence of the gallbladder in delaying the development of bilirubinemia, this observation was recently stressed by Mann and Bollman⁴. Similar and confirmatory results were obtained in this series of experiments.

The maximal degree of bilirubinemia occurred between the first and second week in both series of animals. Thereafter the serum bilirubin gradually decreased, even though complete obstruction was maintained. This is well shown in experiments 1 and 2, in which the

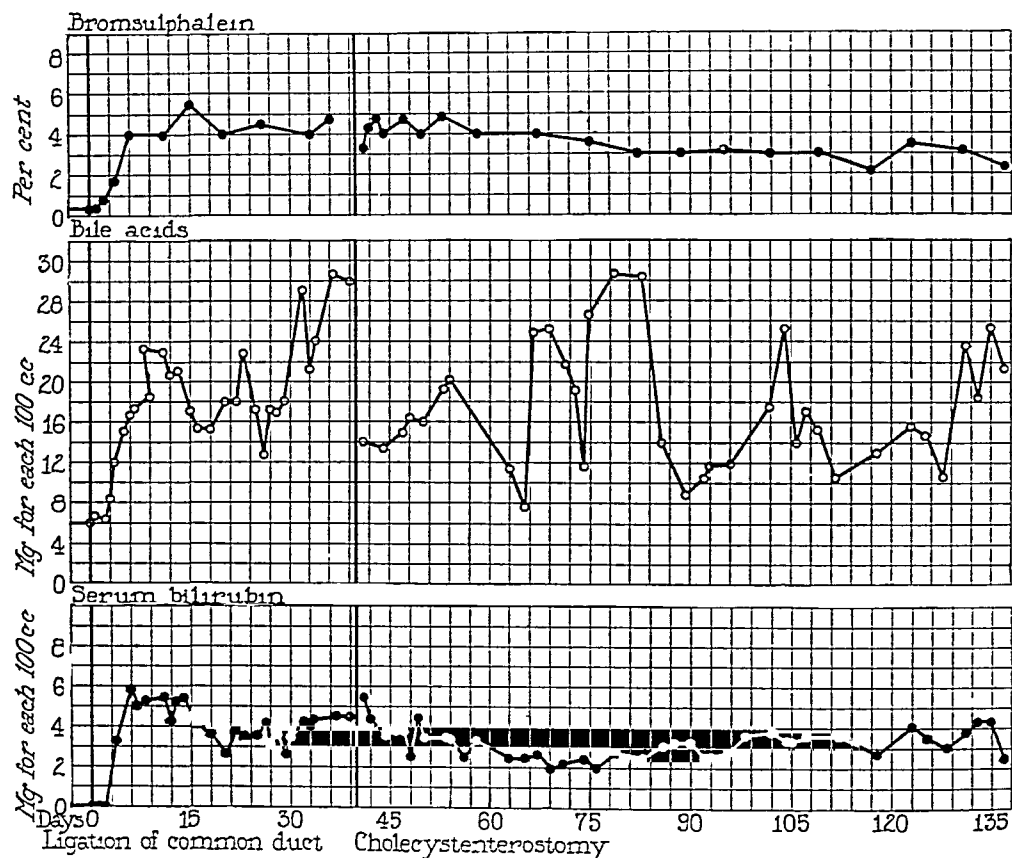


Fig 4 (experiment 3) —Changes in bromsulphalein test, bile acid reading and serum bilirubin following ligation of the common bile duct. Cholecystoduodenostomy was performed on the fortieth day after obstruction.

serum bilirubin decreased spontaneously from 87 to 2 mg, and from 231 to 14 mg, respectively. Associated with the decrease in the serum bilirubin there was a corresponding decrease in the clinical evidence of icterus.

The effect of cholecystenterostomy and consequent reestablishment of biliary drainage apparently varies with the duration of the obstruc-

4 Mann, F. C., and Bollman, J. L. The Relation of the Gallbladder to the Development of Jaundice Following Obstruction of the Common Bile Duct, *J. Lab. & Clin. Med.* 10:540, 1925.

tion With obstruction lasting thirty days or longer, as in these experiments, there was no immediate change in the degree of bilirubinemia after the relief of the obstruction Spontaneous closing of the fistula made it impossible to study the effect of long-continued drainage in such cases

Bromsulphalein—Bromsulphalein⁵ (the disodium salt of phenoltetrabromphthalein disulphonic acid) was used in the present series of experiments in place of the phenoltetrachlorphthalein previously studied

TABLE 4—Changes Observed Following Ligation of the Common Duct and Cholecystectomy (Experiment 4)

Date	Time After Obstruction, Days	Weight, Kg	Hemoglobin, Gm	Nonprotein Nitrogen, Mg, Per Cent	Blood Urea, Mg, Per Cent	Serum Bilirubin, Mg, Per Cent	Van den Bergh Direct Reaction	Bile Acids, Mg, Per Cent	Bromsulphalein Test				
									Dye in Serum, Per Cent				
									5 Minutes	10 Minutes	15 Minutes	1 Hour	2 Hours
1923													
1-6	0	11.5	16.2	28	23	0.0	0	3.8	14	6	2	0	0
1-14	0												
1-16	2	10.7	16.4	18	34	0.7	+	13.1	32	32	30	24	20
1-18	4	10.5	15.0	21	16	2.8	+	15.5	64	56	32	20	10
1-21	7	10.3				4.9	+	10.3	64	60	40	22	20
1-23	9	10.3				3.8	+	7.2	76	72	48	32	20
1-28	11	10.4	14.3	12	16	4.6	+	6.7	76	72	32	28	24
2-1	18	10.4	13.0	35	26	4.5	+	7.7	60	40	30	22	14
2-8	25	10.3	12.0	21	18	4.6	+	12.9	76	60	10	30	20
2-15	32	10.2		13	11	2.8	+	6.0	76	60	30	22	14
2-16	33												
2-20	4	9.2	12.6			3.2	+		40	30	22	16	10
2-22	6	9.1				3.0	+		40	30	22	16	10
2-24	8		12.0	22	10	2.2	+	9.3	40	30	28	16	10
3-1	13	9.4	11.7			1.9	+	7.4	30	22	16	10	10
3-8	20*	9.2	12.0	20	13	1.9	+	9.2	40	28	20	16	16
3-16	28	9.2	12.0	21	14	0.8	+	5.7	30	22	16	12	10
3-22		9.2				0.4	+	6.6	40	26	12	10	4
3-30	11	9.3	12.7	39	17	0.3	+	8.2	36	32	32	16	12
4-5	47	9.7	13.0	35	18	0.3	+	3.6	36	20	14	10	6
4-13	55	9.4	14.8	35		0.0	+	5.3	50	50	32	28	20
4-19	61	9.7		27	20	1.7	+	8.3	60	48	40	30	20
4-27	69			32	29	2.8	+	5.6	60	52	48	36	24
5-4						2.9	+	9.6	60	60	50	42	30

* Intermittent obstruction

The technic of the bromsulphalein test in dogs was the same as that used previously with phenoltetrachlorphthalein. The dye was injected intravenously in a dose of 10 mg. for each kilogram of body weight, twice the dosage used for patients. In thirty determinations on twenty-two normal animals we found that the greater part of the dye disappeared within fifteen minutes. The usual readings of the percentage of dye present in the serum were between 10 and 22 after five minutes with an average of 17, between 3 and 14 after ten minutes, averaging 8, and 6 or less after fifteen minutes. Only traces of dye were found

⁵ Rosenthal, S. M., and White, E. C. (footnote 3, second reference)

in the specimens of blood drawn an hour after its administration. We have compared the results of the different tests on the basis of the reading obtained fifteen minutes after the injection of the dye.

The changes in the bromsulphalein test were qualitatively the same as those previously reported in the phenoltetrachlorophthalein test. Retention of bromsulphalein in the blood stream of the dogs was not observed until the second or third day following ligation of the common bile duct. The development of distinct retention usually coincided with the first definite appearance of bilirubin in the blood, both occurring from forty-eight to seventy-two hours after operation. The

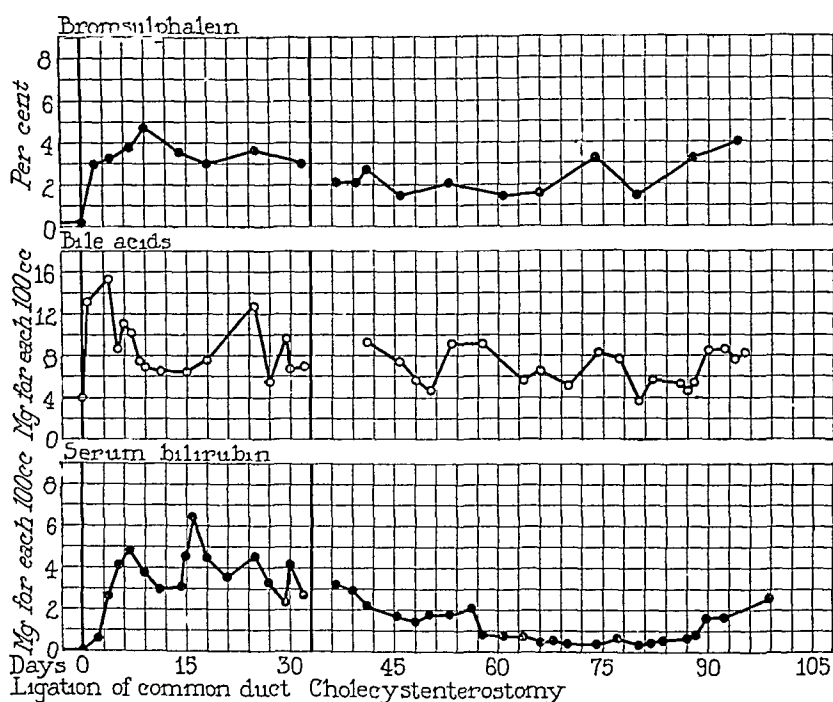


Fig 5 (experiment 4) —Changes in bromsulphalein test, bile acid reading and serum bilirubin following ligation of the common bile duct. Cholecystoduodenostomy was performed on the thirty-third day after obstruction.

amount of retention gradually increased, the maximal value being reached the second week. Thereafter the degree to which the bromsulphalein was retained in the blood stream fluctuated somewhat, but in general there was marked and persistent retention of the dye.

When the gallbladder was removed at the time of the ligation of the common bile duct, retention of the dye was found within twenty-four hours after the operation. Here, too, a close parallelism with the degree of retention of bile was observed. The subsequent course of the two series of animals was identical. Retention of the dye persisted following cholecystenterostomy and the reestablishment of biliary drainage.

Bile Acids.—The bile acids in the blood were determined by the quantitative Pettenkofer reaction developed by Aldrich⁶. The results are reported in terms of milligrams of glycocholic acid for each hundred cubic centimeters of whole blood. The bile acids in the blood, so determined increased markedly after the production of biliary obstruction. This increase was not marked until the second or third day following ligation of the common bile duct alone. Maximal values were attained about the second week after obstruction. When the gallbladder was removed at the time the common duct was ligated, the changes in the bile acid reading developed much more rapidly. The increase was marked within the first hour. The amount of retention in the blood gradually became greater, maximal values being attained at the end of the first week. Thereafter there was a gradual return toward normal. In experiment 1, for example, the bile acids returned to the normal value after fifty days of obstruction. They remained at approximately the normal level thereafter, although the readings were much more variable than in a normal dog. In experiment 2, normal readings were obtained the fifth week. Thereafter considerable fluctuation was observed, although the increases were never so marked as during the week following obstruction.

In experiment 4 the initial rise in the Pettenkofer reading reached a level of only 15.5 mg, then there was a rapid fall. Relief of the obstruction had but little effect, and the values afterward fluctuated between 3.6 and 9.6 mg. In experiment 3, on the other hand, higher values were obtained after the obstruction. There was an increase to 30.8 mg the day before the cholecystenterostomy and a rapid fall to 14.2 mg the day following. The bile acid readings in this dog remained continuously elevated even though the biliary flow was partially reestablished. Here, too, the quantities in the blood showed great fluctuation.

Elimination of Bile Acids.—We have shown elsewhere the rapidity with which bile acids are removed from the blood stream after their timed intravenous injection⁷. In experiment 4 the dog was given such an injection of 200 mg for each kilogram each hour before the ligation of the common duct. This experiment was repeated after the obstruction was established. The comparison of the changes in the blood in the two experiments (fig. 6) shows not only that the bile acids in the blood were more markedly increased by this measure, but also that

6 Aldrich, Martha. Studies in the Metabolism of the Bile Acids. I. A Quantitative Pettenkofer Test Applicable to the Determination of Bile Acids in the Blood, *J. Biol. Chem.*, in press.

7 Snell, A. M., and Greene, C. H. Studies in the Metabolism of Bile Acids. III. The Rate of Elimination of Bile and Its Constituents From the Blood After Their Intravenous Injection, in press.

they were removed at a much slower rate than in the normal. Such a change suggested the possibility of following the curve of elimination of the bile acids as a measure of the functional activity of the liver. Commercial preparations of bile salts were used. These were assayed and given intravenously in a dosage equivalent to 125 mg of glycocholic acid for each kilogram of body weight⁸. The solution was rapidly injected. Samples of blood were then taken, five, fifteen, thirty, forty-five, sixty, and one hundred twenty minutes after the injection.

In normal animals the injected bile acids are rapidly removed from the blood stream. Five minutes after injection the amount varied between 32 and 46 mg, at thirty minutes, between 10 and 23 mg, the normal value for the Pettenkofer reading was regained by the end of the hour.

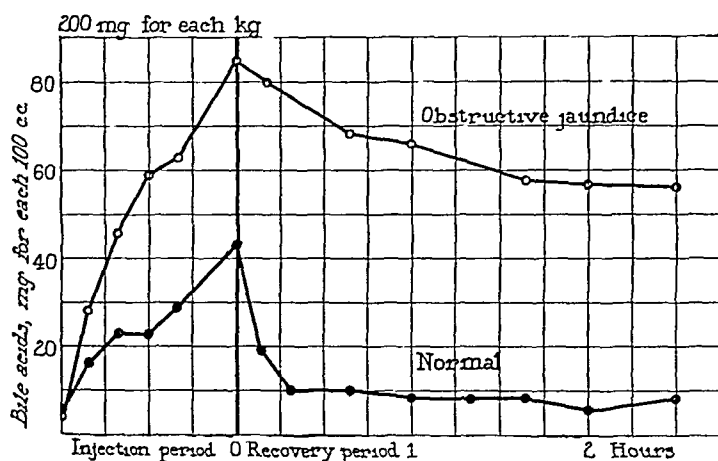


Fig 6—Rate of elimination of bile acids from the blood after their timed intravenous injection. The normal curve and that obtained after the experimental production of obstructive jaundice are shown.

Following the production of biliary obstruction, there was increasing difficulty in the elimination of the injected bile acids from the blood stream. At first (table 5) the bile acids failed of elimination within the usual time, and high readings were obtained an hour and two hours after the injection. Later, not only was there great delay in excretion, but the whole level of the curve was also increased to nearly double the initial reading. In one instance the amount in the blood five minutes after injection was 80.5 mg, and two hours later, 37.5 mg. This is shown graphically in figure 7, which presents the changes in another animal.

⁸ Bledsoe, Mary Sue, Aldrich, Martha, and Greene, C. H. Studies in the Metabolism of the Bile Acids. II. The Estimation of Bile Acids in the Bile, *J. Biol. Chem.*, in press.

Although injections were made every second or third day, there was no evidence of an accumulation of bile acids within the body. The quantities injected were apparently either eliminated through the urine or else destroyed. The experiments of Brakefield and Schmidt⁹ on the changes in the urine following biliary obstruction demonstrate the urinary excretion of injected bile acids, and so support the former view.

COMMENT

The changes observed in obstructive jaundice in this series of experiments confirm and extend observations made in our earlier paper. The decrease in the blood urea, especially in relation to the nonprotein nitrogen in the blood, is definite although not marked.

TABLE 5—Changes Observed Following Ligation of the Common Bile Duct*

Date	Time After Obstruction, Days	Hemoglobin, Gm	Nonprotein Nitrogen, Mg, Per Cent	Blood Urea, Mg, Per Cent	Serum Bilirubin, Mg, Per Cent	Van den Bergh Direct Reaction	Bromsulphalein Test					Elimination of Bile Salt, Time After Injection					
							Dye in Serum, Per Cent										
							5 Minutes	10 Minutes	15 Minutes	1 Hour	2 Hours	Control	5 Minutes	15 Minutes	30 Minutes	1 Hour	2 Hours
1926							Mg for each 100 cc										
11-18	0		21	28	0	0	6	2	2	0	0	6.6	36.3	26.2	10.2	6.5	6.1
11-19	0	14.7	32	28													
11-23			Ligation of common bile duct														
11-24	1	13.7	24	8	0	0	30	22	22	22	14						
11-25	2											8.6	41.1	31.2	27.0	27.0	23.4
11-26	3	8.9	33	22	1.8	+	40	30	30	20	12	11.5	65.6	60.0	54.3	45.1	27.8
11-27	4																
11-29	6	12.0	41	16	2.3	+	60	40	30	20	15						
11-30	7											9.7	80.5	51.9	48.4	38.2	37.5
12-3	11	13.2	34	16	3.7	+	60	35	35	16	12						
12-4	12											15.6	71.5	62.1	53.4	43.2	25.8
12-6	14											11.0	63.0	47.3	38.8	24.4	29.6
12-8	16		35	17	2.8	+	60	30	22	12	10						

*Experiment not described

The changes in the serum bilirubin during the first few days after obstruction of the common bile duct are determined largely by the presence or absence of the gallbladder, as recently stressed by Mann and Bollman.¹ We were able to keep some of these dogs with complete biliary obstruction alive and in good condition for a considerable period. After the first few weeks, such animals showed a gradual decrease and almost complete disappearance of the jaundice. At the same time, there was a gradual reduction in the serum bilirubin to a level of from 1 to 3 mg. This reduction is not due to increased renal elimination of pigment, for Brakefield and Schmidt⁹ have shown the

9 Brakefield, J. L., and Schmidt, C. L. A. Studies on the Synthesis and Elimination of Certain Bile Components in Obstructive Jaundice, *J. Biol. Chem.* 67: 523, 1926.

gradual diminution in the urinary output of bilirubin in obstructive jaundice. A similar condition is observed in patients. In cases of obstructive jaundice of short duration, as from carcinoma of the head of the pancreas, higher serum bilirubin values occur, as a rule, than in cases of long-standing obstruction, as from stone in the common duct. There are numerous exceptions, but both the clinical and experimental evidence suggests that the production of bilirubin is decreased in consequence of prolonged biliary obstruction. In some cases this may be related to the reduction in the hemoglobin, as suggested by Rous and Drury¹⁰. On the other hand, we do not feel that the hemoglobin content of the blood is necessarily an accurate index to the degree of physiologic wastage of corpuscles, or the sole controlling factor in pigment metabolism.

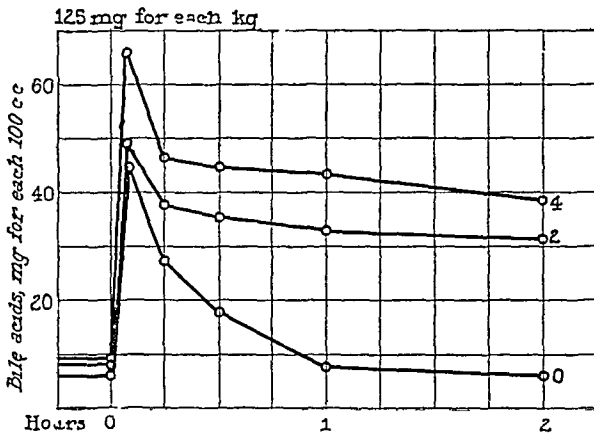


Fig 7—Change in the rate of elimination of bile acids from the blood during the development of obstructive jaundice. The bile salt solution was injected rapidly. The figures indicate time in days after ligation of the common bile duct and removal of the gallbladder.

The changes in the bromsulphalein test conform accurately to those previously obtained by the use of phenoltetrachlorophthalein. In each case retention of dye developed to an extent apparently conditioned by the rate of development and degree of the retention of the bile. With long-standing obstruction, retention of dye was relatively more marked and did not decrease as did the bilirubin level in the serum. The injection of bromsulphalein does not produce thrombosis of the vein as readily as does phenoltetrachlorophthalein. It also seems to be somewhat more sensitive to slight changes in the liver, hence bromsulphalein is preferable for routine clinical use.

The identification of bile acids in the blood on the basis of a colorimetric test such as the Pettenkofer reaction is open to criticism because

10 Rous, P, and Drury, D R. Jaundice as an Expression of the Physiological Wastage of Corpuscles, *J Exper Med* **41** 601, 1925

this reaction is not wholly specific. The presence of bile acids in the blood in obstructive jaundice has been accepted since the early experiments of Kuhne¹¹ and Huppert¹². More recently Perlzweig and Barron¹³ reported positive colorimetric tests for bile acids in the blood of patients with obstructive jaundice, while Rosenthal and Wislicki¹⁴ have obtained similar results with a modification of the amino-acid determination of Foster and Hooper. These results, together with the accepted fact of the urinary excretion of bile acids in this condition, furnish sufficiently direct evidence to justify our assumption that, in obstructive jaundice, the changes in the Pettenkofer reaction may be used as an index to changes in the amount of bile acids in the blood.

The bile acids in the blood, as determined by this method, increase temporarily after the production of biliary obstruction. The amount in the blood may be increased for two weeks, but it then decreases, and the normal values for the blood are gradually regained. Malkoff,¹⁵ and Brakefield and Schmidt⁹ have demonstrated that the curve of urinary excretion of the bile acids in obstructive jaundice shows similar changes. They point out that in this condition injected bile acids are largely, though not quantitatively, excreted in the urine. They further point out that the urinary output of bile acids in animals with obstructive jaundice is only a small fraction of the normal or of that which a dog with a biliary fistula can synthesize. From this they conclude that as a result of biliary obstruction there is a decreased synthesis rather than an increased breakdown of taurocholic acid.

Our experiments are in agreement with this view. The rapidity with which injected bile acids are removed from the blood stream of normal animals will explain their failure to appear in the urine in the control experiments of Brakefield and Schmidt. Biliary obstruction and stasis promptly blocks the normal pathway of excretion, and injected bile acids then leave the blood at a much slower rate than normally. In these experiments the amount injected was too small to cause permanent retention. If this was not completely excreted by the kidneys, the body was presumably able to destroy the excess. It should be noted, however, that the injected bile salts were not without toxic

11 Kuhne, W. Beitrage zur Lehre vom Icterus. Eine physiologisch-chemische Untersuchung, *Arch f path Anat u Physiol* **14** 310, 1858.

12 Huppert, H. Ueber das Schicksal der Gallensauren im Ikterus, *Arch f Heilkund* **5** 236, 1864.

13 Perlzweig, W. A., and Barron, E. G. New Colorimetric Method for the Determination of Bile Acids in Blood, *Proc Soc Exper Biol & Med* **24** 233, 1926.

14 Rosenthal, F., and Wislicki, L. Ueber eine quantitative Bestimmung der Gallensauren im Blute, *Arch f exper Path u Pharmakol* **127** 8, 1926.

15 Malkoff, G. Zur Pathologie des Ikterus. Ueber die Ausscheidung der Gallensauren durch den Harn, die Bauchwassersucht und einige andere Erscheinungen bei der Gallenretention, *Jahresb u d Fortschr d Thierchem* **27** 785, 1897.

action, for animals so treated were not in as good condition and did not live as long as the other dogs in this series

Reference should also be made to the biliary cirrhosis which developed in all the dogs that survived for more than a few weeks. The morphologic changes are too well known for especial comment. The functional changes recorded serve to explain some of the difficulties with cholecystenterostomy in these animals. In two dogs an attempt was made to relieve the biliary obstruction on the thirtieth and fortieth day, respectively. In neither did the bromsulphalein test show improvement following cholecystenterostomy. The serum bilirubin decreased a little, but the change was slightly, if any, more rapid than in those animals in which the obstruction persisted. The bile acids rapidly return toward normal after relief of the obstruction. This too may be related to the spontaneous decrease observed in all animals. The extremely rapid fluctuations in the bile-acid level observed in experiment 3, in which there was a period of intermittent obstruction, suggest that they are rapidly removed from the blood with the reestablishment of the biliary flow. Such an observation would be in harmony with the recognized normal rapidity of excretion of injected bile salts.

The development of ascites, collateral circulation and other evidences of portal obstruction which occurred in two animals in our series, as in the dog reported by Malkoff, is of much clinical and experimental interest. The ascites seen in such long-standing obstructive biliary cirrhosis is related to the widespread proliferation of connective tissue around the biliary radicals in the portal spaces, with consequent obstruction to the portal venous return. Malkoff further postulates changes in the blood as an additional factor predisposing to ascites. Mangelsdorf,¹⁶ Ford,¹⁷ and Weber,¹⁸ have described the development of ascites in the terminal stages of biliary cirrhosis in consequence of continuous and prolonged biliary obstruction in man, and we have seen such cases. These animal experiments furnish the counterpart to this clinical condition.

SUMMARY

The effect of ligation of the common bile duct in dogs and the consequent experimental production of obstructive jaundice have been studied in more detail than was possible at the time of our original report. It was possible to keep two dogs with complete biliary obstruction alive for more than three months. In these dogs an extensive collateral circulation and ascites developed, thus providing an experimental

16 Mangelsdorf, J. Ueber biliare Lebercirrhose, *Deutsches Arch f klin Med* **31** 522, 1882

17 Ford, W. W. Obstructive Biliary Cirrhosis, *Am J M Sc* **121** 60, 1901

18 Weber, F. P. On Biliary Cirrhosis of the Liver With and Without Cholelithiasis, *Tr Path Soc London* **54** 103, 1903

counterpart of the advanced biliary cirrhosis seen clinically in association with prolonged biliary obstruction

During the period immediately following ligation of the common duct, the changes in the blood urea, serum bilirubin and the degree of retention of dye were similar to those previously reported. The effect of the presence or absence of the gallbladder in determining such changes was shown to hold, not only for the bilirubin but also for the bromsulphalein test and for the bile acids in the blood.

The bilirubin content of the serum tends to decrease spontaneously in the later stages of obstructive jaundice, presumably due to a decrease in the production of pigment. With the development of cirrhotic changes in the liver the excretion of bilirubin apparently becomes increasingly difficult, and in two dogs cholecystenterostomy with temporary relief of the biliary obstruction did not significantly affect the level of bilirubin.

The changes in the bromsulphalein test were in entire agreement with those previously obtained with phenoltetrachlorophthalein. The retention of dye in its development closely paralleled the degree of retention of bile. Once retention was established, the bromsulphalein readings were relatively constant and its retention more persistent than that of either the bile acids or the bilirubin.

The intensity of the Pettenkofer reaction given by the blood increased rapidly after obstruction. The rate of accumulation of bile acids under these circumstances was determined by the activity of the gallbladder, as in the case of the bilirubin. Later the readings tended to decrease, and returned approximately to the normal value, indicating probable failure of the synthesis of the bile acids. The changes in the blood corresponded with the reported changes in the urinary excretion of the bile acids. We believe, therefore, that the changes in the Pettenkofer readings may be considered indicative of changes in the bile acid content of the blood.

Intravenously injected bile acids are rapidly removed from the blood stream of normal animals. This elimination was interfered with in obstructive jaundice, and injected bile acids were retained in the blood stream, the degree of retention paralleling the changes in the other tests.

These experimental data are a counterpart of, and in agreement with, the changes observed clinically in obstructive jaundice and in biliary cirrhosis secondary to obstruction of the bile passages.

NORMAL VARIATIONS IN WHITE BLOOD CELLS UNDER CONDITIONS OF MINIMAL METABOLISM *

RICHARD P STETSON, M D

BOSTON

The white blood cells of normal persons have been the subject of many and varied forms of investigation since they were first described in 1777 by Hewson ¹. As a consequence, limits of normal have been established both for the total numbers per cubic millimeter of circulating blood and for the percentages of the types of cells comprising this total. These normal limits have been determined from observations made once on each of a group of healthy persons or from data obtained by repeated observations of the same person's blood over a period of hours. The influence of various physiologic processes on the white blood cell picture has also been studied extensively. However, comparatively little information is available concerning the fluctuations of the nucleated blood cells that may occur over an extended period of time in a normal person. Such observations as have been made appear not to have been conducted under conditions of minimal metabolism.

The fluctuations occurring during the day have been repeatedly studied. Turk ² considers, as do others, that the white blood cell count is at a minimum in the early morning, when the person is at complete rest and before the ingestion of food. Then it may be below 5,000 cells per cubic millimeter, with a marked depression of polymorphonuclear neutrophils and a relative abundance of lymphocytes, often amounting to from 30 to 40 per cent of the total and sometimes more. Mauriac and Cabonat ³ also found that the greatest constancy in the absolute and differential white blood cell count occurred in the early morning. Like others, they record a marked fluctuation during the day. Sabin and her

* From the Medical Service of the Collis P. Huntington Memorial Hospital of Harvard University. This work was aided by a grant from the Proctor Fund of the Medical School of Harvard University for the study of chronic disease.

1 Hewson, William. A Description of the Particles of the Blood in the Human Subject and in Other Animals with an Account of the Structure and Offices of the Lymphatic Glands, of the Thymus Gland, and of the Spleen, London, 1777. From the Works of William Hewson, F. R. S., edited by George Gulliver, Sydenham Society, 1846, p. 251.

2 Turk, W. Vorlesungen über klinische Hämatologie, Wien, W. Braumüller, 1912, vol. 2.

3 Mauriac, P., and Cabonat, P. Contribution à l'étude des variations de la formule leucocytaire chez l'homme normal, Paris med. **11** 407 (May 21) 1921.

associates,⁴ in a systematic study of several persons over periods of hours, have demonstrated a characteristic and approximately hourly rhythm of the circulating white blood cells which is independent of digestion or exercise. They found that the total white blood cell count might vary as much as 100 per cent in the course of the day. The higher values were obtained in the afternoon and were largely due to increases in the polymorphonuclear neutrophils. Other types of cells showed characteristic, although less extreme, rhythmic fluctuations. Somewhat similar observations have been recorded by other investigators.⁵

Appreciable variations in the absolute numbers of white blood cells have been noted in counts of blood taken at approximately the same hour on successive days. Spiethoff⁶ and Michailow⁷ reported that this variation was frequently as great as 2,000 cells per cubic millimeter. They found, however, that the percentage relationships of the various types of cells were remarkably constant and that no reciprocal relationship occurred between the polymorphonuclear neutrophils and lymphocytes. Heintz and Welker,⁸ on the other hand, showed a greater constancy in the daily total white blood cell count of twenty-two normal subjects whose blood was examined at approximately the same hour each morning soon after breakfast for a seven-day period. Their counts demonstrated an average daily fluctuation of only about 300 cells per cubic millimeter and a maximum difference of 1,600 per cubic millimeter in any one subject during the entire period of observation. These variations are hardly beyond those which may be accounted for by probable error.

4 Sabin, F. R., Cunningham, R. S., Doan, C. A., and Kindwall, J. A. The Normal Rhythm of the White Blood Cells, *Bull. Johns Hopkins Hosp.* **37** 14 (July) 1925.

5 Spiethoff, B. Besteht nach die Kriegllymphocytose, *Munchen med. Wchnschr.* **69** 1532 (Nov. 3) 1922, Zur Methode der Blutuntersuchungen und Mitteilungen über fortlaufende Blutuntersuchungen an Gesunden, *Folia haemat.* **32** 325 (July) 1926. Kobryner, A. La leucocytose physiologique chez l'homme, *Compt. rend. Soc. de biol.* **90** 1475 (June 6) 1924, Über den physiologischen Verlauf der Leukozytose beim Menschen, *Deutsche med. Wchnschr.* **50** 1218 (Sept. 5) 1924, Physiologic Course of Leukocytosis in Man, *Ztschr. f. klin. Med.* **102** 470, 1925. Glaser, F., and Buschmann, P. Die Bedeutung der Spontanschwanungen der Leukozyten (besonders für die hamoklasische Krise und die Verdauungsleukozytose), *Med. Klin.* **19** 1144, 1923. Jimenez Diaz, C., Espejo, M., and De Avellaneda, G. Leukocyte Variation Curve and its Significance, *Arch. de Cardiología y Hematología* **6** 1118, 1925. Woronoff, A., and Riskin, J. Ueber die Leukozytose bei normalen Menschen und Hunden, *Wien. Arch. f. inn. Med.* **10** 45 (April) 1925.

6 Spiethoff. Footnote 5, second reference.

7 Michailow, F. Die Schwankungen der Leukozytenzahl und Leukozytenformel im peripherischen Blute des Menschen und die Verdauungsleukozytose, *Folia haemat.* **32** 196 (May) 1926.

8 Heintz, E. L., and Welker, W. H. The Effect of the Ingestion of Yeast on the Leukocyte Count, *Arch. Int. Med.* **35** 500 (April) 1925.

It is evident that the white blood cell formula is by no means a fixed ratio, but may be subject to appreciable changes during the day and from day to day even under standard conditions. In evaluating counts of the blood cells, one must appreciate not only the degree and kind of physiologic variations and the technical error of the methods, but also the mathematical error arising from the numbers of cells counted. This has been fully discussed recently by Brandt,⁹ who allows a range of about 30 per cent in the total white blood cell count as being the limit of "fortuitous error." Consistency in repeated observations must be considered significant, however, even in the absence of absolute mathematical certainty.

The present study was undertaken to observe any degree of constancy that might be obtained over an extended period of time in the daily total and differential white blood cell count of normal persons under conditions of minimal metabolism.

MATERIAL AND TECHNIC

The subjects were six healthy medical students in the third decade of life, who were living hygienically under comparative conditions. Their blood was obtained in the morning before they got out of bed, except as noted below. The blood of two (A and B) was examined approximately every other day for six weeks in the late autumn, that of the others (C, D, E and F) was examined every day for ten days during the month of February. Every other day for periods of weeks at different times of the year, smears were also made of A's blood immediately after he had arisen.

The blood for the white blood cell counts and cover glass smears was taken from the finger of A and from the lobe of the ear of the other persons. A minimum amount of manipulation was employed in obtaining the blood, and the same pipet and hemocytometer were used in counting each person's blood. Careful attention was given to following the recognized technic for an accurate count of the corpuscles and the preparation of evenly spread films of blood. All enumerations were made by the same person. Never less than 200 cells, usually 400 and sometimes more, were counted from the two coverslips made at one time to determine the percentages of the different types of cells. Five classes of cells were recorded: polymorphonuclear neutrophils, eosinophils, basophils, lymphocytes (small, large and atypical) and monocytes. Fragmented forms were not included. The rare observations of certain immature forms were listed separately.

9 Brandt, T. Ueber die Fehlerberechnung der hamatologischen Methoden, ein Beitrag zur kritischen Beurteilung der gefundenen, Werte, *Folia haemat* 32 177 (May) 1926.

Tables 1 and 2 summarize the results of the white blood cell counts on the six students under conditions of minimal metabolism

Charts 1 and 2 illustrate graphically the variations in the differential and absolute enumerations of the white blood cells of student D. The graphs for D are entirely comparable to those for the other subjects, although some showed slightly more and some less daily variation in the counts

TABLE 1—Ten to Fourteen Daily White Blood Cell Counts of Six Normal Persons Under Conditions of Minimal Metabolism

Individual	White Blood Cells (*)		Polymorphonuclear Neutrophils (†)		Lymphocytes (‡)		Monocytes	
	Per		Per		Per		Per	
	Cu Mm	Cent	Cu Mm	Cent	Cu Mm	Cent	Cu Mm	Cent
A	Av	6,700	3,690	53.6	2,219	33.7	618	9.3
	Min	5,000	2,121	46.5	1,842	29.0	332	5.0
	Max	7,700	4,750	61.5	2,584	39.0	840	12.0
B	Av	5,832	3,034	51.4	2,183	37.0	459	7.8
	Min	4,800	2,290	45.0	1,765	29.5	234	4.5
	Max	7,150	3,680	58.5	2,860	45.0	793	12.0
C	Av	5,547	2,845	51.3	1,838	33.2	630	11.3
	Min	4,975	2,310	40.5	1,477	27.2	277	5.5
	Max	6,450	3,775	62.7	2,306	40.7	908	14.7
D	Av	7,425	3,726	50.3	2,706	36.4	781	10.5
	Min	5,125	2,760	44.0	1,860	29.7	502	8.5
	Max	9,550	5,110	57.7	4,020	44.0	1,048	12.2
E	Av	4,987	2,723	54.7	1,662	33.3	500	10.0
	Min	4,050	2,154	50.5	1,293	30.2	360	8.0
	Max	7,150	3,510	58.2	2,573	36.5	786	12.0
F	Av	7,632	3,451	45.3	3,192	41.8	729	9.5
	Min	6,800	2,975	39.7	2,312	33.5	527	7.7
	Max	9,025	4,075	55.0	3,801	48.0	930	11.0

* While the maximum variation in no case occurred between consecutive counts, there was frequently a variation of 1,800 cells per cubic millimeter from one day to the next

† For purposes of condensation, the values for polymorphonuclear eosinophils and basophils have been omitted from this table. The former varied between 0 and 5.2 per cent, the latter between 0 and 3.5 per cent. The averages are shown in table 2

‡ The large lymphocytes usually formed about 4 per cent of all the white blood cells

TABLE 2—Averages and Extremes of All Counts (62) on All Six Persons

	POLYMERIZATION OF VINYL MONOMERS												
	POLYMERIZATION OF VINYL MONOMERS												
	POLYMERIZATION OF VINYL MONOMERS												
	POLYMERIZATION OF VINYL MONOMERS												
	White Blood Cells		Polymorpho- nuclear, Neutrophils		Eosinophils		Basophils		Lymphocytes		Monocytes		
	Per Cu Mm	Per Cu Mm	Per Cent	Per Cu Mm	Per Cent	Per Cu Mm	Per Cent	Per Cu Mm	Per Cent	Per Cu Mm	Per Cent	Per Cu Mm	Per Cent
Av	6,309	3,216	51 04	148	2 31	55	0 85	2,294	36 04	609	9 62	231	4 50
Min	4,050	2,154	39 75	00	0 00	00	0 00	1,293	27 25	231	4 50	231	4 50
Max	9,550	5,110	62 75	407	5 25	241	3 50	4,020	48 00	1,048	14 75	1,048	14 75

Variations in the total white blood cell counts from day to day were often greater than 1,000 and even as great as 2,400 cells per cubic millimeter. The extreme variation shown by any one person during the entire period of observation was 4,125 cells per cubic millimeter, while the least maximum variation was 1,475. A variation of 1,000 per cubic millimeter in the number of white blood cells when the total number is about 7,000 is not mathematically significant. However, variations occurred greater than the mathematical error, and the constant fluctuation from day to day cannot be explained as due to technical

or mathematical errors. The degree of these fluctuations in the numbers of white blood cells under conditions of minimal metabolism is not as great as has been observed in relatively inactive persons throughout the day.

The fluctuations in the total number of white blood cells was not dependent on any one type of cell, although the polymorphonuclear neutrophils perhaps owing to their greater frequency, exerted the most apparent effect. The percentage of polymorphonuclear neutrophils was found to be considerably lower than the commonly accredited figures (about 60 per cent) for normal persons in this locality. The values

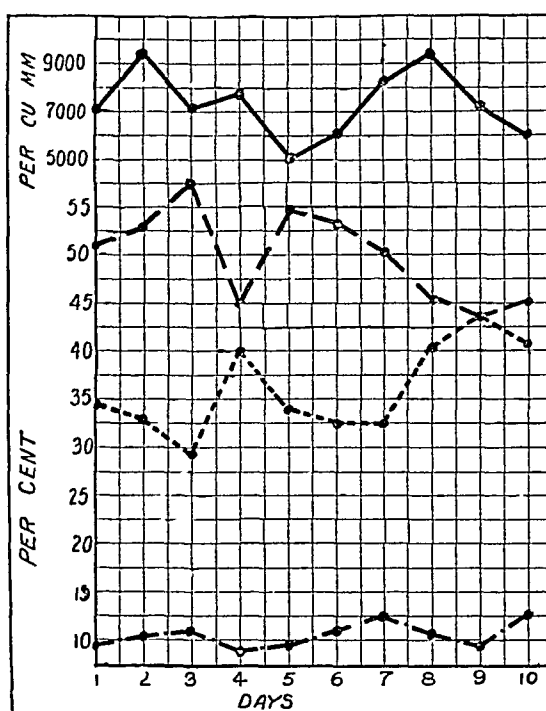


Chart 1—Daily variations in the percentages of white blood cells in a normal individual (D) under conditions of minimal metabolism. The solid line represents the total of white blood cells per cubic millimeter, the broken line represents the percentage of polymorphonuclear neutrophils, the dotted line, the percentage of lymphocytes, and the dot and dash line, the percentage of monocytes.

ranged from 39.7 to 62.7 per cent, the average for all counts being 51.04 per cent. If a deviation of 5 per cent is allowed on either side of this average as due to "fortuitous error," many of the variations shown by these subjects are to be interpreted as an actual change in the number of cells. The same is true for the fluctuating percentage of lymphocytes, which ranged from 27.2 to 48 per cent, the average being 36.04 per cent. The general trend of these figures is in accordance with those obtained by Turk² and others who have observed that before breakfast there is a smaller percentage of polymorphonuclear elements and a

greater percentage of lymphocytes in the circulating blood than later in the day

The fluctuations that occurred among the other types of normal white blood cells were slight and require no comment. Myelocytes have been observed occasionally in the blood of normal persons as, for example, by Sabin⁴ and her co-workers. Such cells were found infrequently in this series of observations. Atypical cells, apparently of lymphoid origin, were encountered on five occasions.

Chart 3, besides illustrating the daily fluctuations that occurred in the differential white blood cell formula of one person (A), also shows

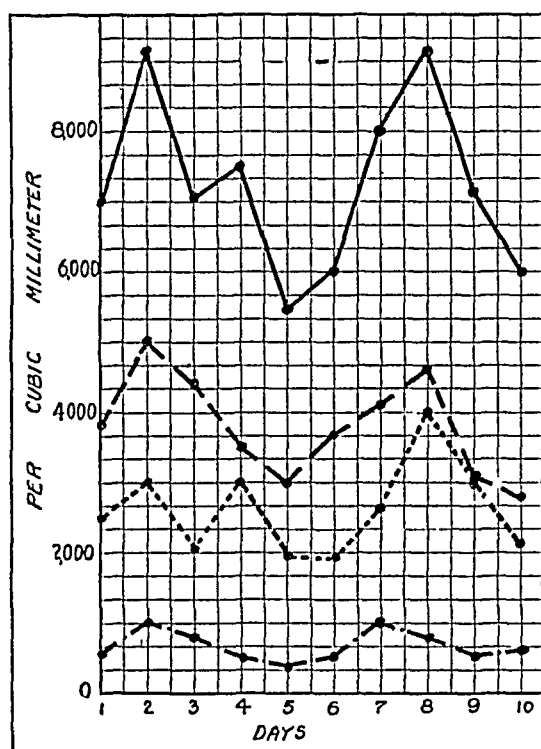


Chart 2—Daily variations in the absolute numbers of white blood cells per cubic millimeter under conditions of minimal metabolism. The percentage values of the same counts are recorded in figure 1. The continuous line in this chart represents the total of white blood cells per cubic millimeter, the broken line, the polymorphonuclear neutrophils per cubic millimeter, the dotted line, the lymphocytes per cubic millimeter, and the dot and dash line, monocytes per cubic millimeter.

the definite change observed in the relative frequency of polymorphonuclear neutrophils and lymphocytes over a period of months. There was a slight, but consistent decrease in the percentage of polymorphonuclear neutrophils with a relative increase of lymphocytes for a period of time in the autumn and early winter as compared with the values obtained in the late spring, summer and midwinter. The period showing the highest average percentage (63.24) of polymorphonuclear neutrophils was in June. At that time, the lymphocytes averaged 25.86 per

cent The lowest average percentage (47.8) of neutrophils occurred in December when the lymphocytes averaged 38.67 per cent This difference in values appears to be of sufficient magnitude to be mathematically significant

Exposure to the sun's rays induces an increase of lymphocytes¹⁰ This can account for the increase in lymphocytes observed by Taylor¹¹ in twenty-five of the thirty-eight persons studied by him before and after they had spent a summer at Woods Hole, Mass The increase of lymphocytes recorded in white people in the tropics or in the Philippines¹² may also be attributed partially to sunlight Thus, the effect of sunlight may be a seasonal factor in influencing the differential white

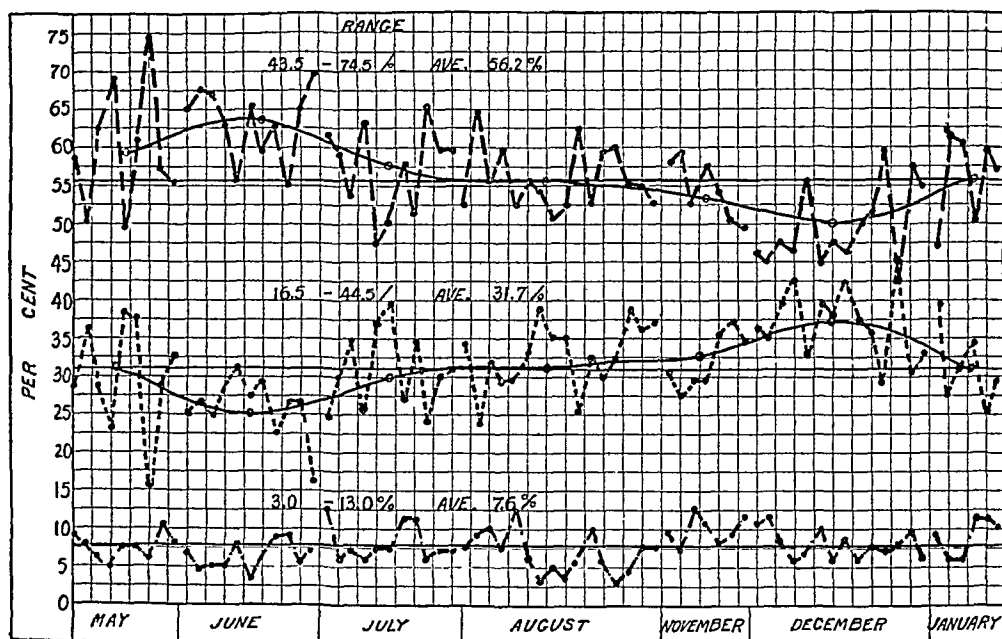


Chart 3—Variations in the percentages of the white blood cells of one individual (A) under conditions of minimal metabolism over a period of months The broken line represents the polymorphonuclear neutrophils, the dotted line, the lymphocytes, and the dot and dash line, the monocytes The straight heavy lines represent the averages for the whole series of counts (74) The continuous curved lines connect the points representing the averages of the several periods

blood cell count, but it seems unlikely that this is the factor responsible for the increase in lymphocytes noted during December in the observations recorded here Alterations in the white blood cell formula during

10 Clark, J H Action of Light on the Leukocyte Count, *Am J Hyg* 1 39 (Jan) 1921 Aschenheim, E Der Einfluss der Sonnenstrahlen auf die leukocytaire Blutzusammensetzung, *Ztschr f Kinderh* 9 87, 1913

11 Taylor, H D The Effect of Exposure to the Sun on the Circulating Lymphocytes in Man, *J Exper Med* 29 41 (Jan) 1919

12 Wallace, J B The Differential Leucocyte Count in a Sub-Tropical Climate, *South M J* 17 827 (Nov) 1924 Wickline, W A The Effects of Tropical Climate on the White Race, *Mil Surgeon* 23 282, 1908

the various seasons of the year are of interest to speculate on, but the relatively scanty data at hand and the lack of other similar observations preclude drawing conclusions

It is known that ingestion of lecithin will produce a transient lymphocytosis,¹³ while a relatively high percentage of lymphocytes is not rare in obese persons¹⁴ The question thus arose as to whether a diet rich in fat could maintain the percentage of lymphocytes at a relatively high level In an effort to answer this question, subject A took a daily diet consisting of fat, 190 Gm, protein, 86 Gm, and carbohydrate, 200 Gm, for nine days in June and for five days in December This diet contained approximately twice the amount of fat eaten during the other periods of observation Although not deliberately chosen, it happened that the diet rich in fat was taken during the periods when the average of lymphocytes was at a low level (June) and at a high level (December) However, the diet as taken did not result in any increase of lymphocytes attributable to the fat This negative observation by no means precludes the possibility that a diet rich in fat taken for a long period of time may induce an increase of lymphocytes in certain people

SUMMARY

The white blood cells of six normal persons under conditions of minimal metabolism were studied daily for ten days and the white blood cells of one of these persons were observed frequently in each of several months of the year

The following conclusions are reached

- 1 The polymorphonuclear neutrophils were fewer and the lymphocytes greater than usual during the day The average percentage of the former was 51.04 and of the latter, 36.04

- 2 Daily variations in the white blood cell count were beyond the limits dependent on technical or mathematical errors Each type of cell shared in the fluctuations

- 3 The average percentage of polymorphonuclear neutrophils and lymphocytes maintained different levels during different periods of the year

- 4 Immature cells of both myeloid and lymphoid origin were encountered rarely

¹³ Bain, William The Pharmacology and Therapeutics of Lecithin and Phytin, *Lancet* **1** 918 (April 6) 1912

¹⁴ Caro, L Blutbefunde bei Adipositas, *Berl klin Wchnschr* **49** 1881 (Sept 30) 1912

NATURAL MINERAL WATERS IN THE LIGHT OF MODERN RESEARCH

THE CATALYTIC ACTION OF THE SARATOGA SPRINGS *

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This paper deals chiefly with a report of chemical and physico-chemical observations on mineral springs. We shall attempt to demonstrate that, through the discovery of new methods, the study of mineral springs has entered a new epoch. Long before the development of quantitative chemical analysis, mineral springs were empirically employed, with good results, in the treatment of many diseases. New aspects manifested themselves, however, when the chemist began to analyze the springs and to establish the nature and quantity of the salts contained in them. At first, naturally, chemical analysis was not well developed, and it was difficult, therefore, to demonstrate with certainty the presence of minute traces of elements. In this connection it is of interest to note that salt springs in Austria, which were traditionally known as "goiter-waters," appeared to contain only common salt until modern analytic chemistry showed that they also contained the therapeutically active iodine. There are many cases known in which man's instinct first found the remedy, while science, with its exact explanations, lagged behind. The classic example of this in balneology is the early recognition of curative springs which seemed to contain ordinary drinking water, but which later, after the discovery of radium, proved to be strongly radioactive.

SIGNIFICANCE OF TRACES OF ELEMENTS IN BIOLOGIC PROCESSES

In these examples we are confronted with the remarkable fact that the active substance of a curative water may be present in extremely small amounts, and that often only slight traces of a substance suffice to bring about profound biologic changes in animals and in man. Every thinking physician who would keep abreast of modern science must be conversant with the idea that amounts of substances which are hardly weighable and perhaps often only spectroscopically detectable are capable, under certain circumstances, of exerting great biologic effects and are therefore, of therapeutic significance. In this respect, modern research on vitamin has taught us much that is astonishing.

*From the Laboratories of the Rockefeller Institute for Medical Research

There is a broad and still virgin field in the investigation of the biologic action of the numerous substances in natural mineral waters, many of which are present only in traces. In the latter class is iron, an element widely distributed in nature. Iron often accumulates in considerable quantities in mineral springs, thus, the Moritz spring in Bad Elster, one of the strongest, iron-carbonic acid springs, contains 26 mg of iron per liter¹. The question of the rôle of iron in metabolic processes has acquired increasing importance in recent years. The metabolism of iron is more complicated than was formerly assumed, for contrary to other inorganic substances, resorbed iron is not carried directly to the site of its utilization, nor is waste iron directly eliminated. Stores of this element exist in the spleen, liver and bone marrow. In iron-free nutrition, serious anemia does not occur until from the second to the fourth generation. Long before the chemical determination of iron in mineral waters, these were successfully employed as remedies for anemia. The blood contains iron as an integral constituent, and by means of this element binds the oxygen of the air and transports it, apparently in mildly activated condition, to the sites of its utilization.

Respiration, which many physiologists designate, in concordance with Barnes, as "energenesis," is, according to the new physiologic point of view, the most important of metabolic processes in the human organism. According to Warburg, iron is indispensable to respiration. Further, iron together with magnesium-containing chlorophyll is the transporter of solar energy in the reduction of carbonic acid by green plants—that fundamental, life-sustaining process of our planet. The oxidation of ferrous bicarbonate to ferric carbonate can serve as a source of energy for those lower plants which assimilate carbonic acid chemosynthetically.

These few examples should suffice to illustrate the great significance of iron in biologic processes. From a purely chemical and physical point of view also, iron is distinguished from all other elements particularly by its complex spectrum which signifies a large number of electron shifts, and further, by its special magnetic behavior. Of the many chemical peculiarities of iron, the one that interests us here above all is the catalytic properties of the metal, its salts and oxides. In our own research the catalytic properties of the iron dissolved in mineral waters were studied, and we shall report the results of our investigation in this article.

Before we describe our new experiments and discuss the significance of the constitution of a salt in relation to its catalytic and biologic properties, we shall first analyze, in a general way, the conditions of

1 Leidner, Tustus. Dissertation, Berlin, 1916. Bickel, Adolf, Gledmann, F., and Taslakowa, T. *Ztschr f d ges exper Med* 54 87, 1927.

forms in which the individual constituents of so complex a salt mixture as a natural mineral water can theoretically come into play. The inorganic substances can occur in various states, and the following classifications may be used as a guide:

- 1 Ions (electrically charged atoms of the elements)
- 2 Complexions (in the Werner sense)
- 3 Undissociated molecules²
- 4 Colloidal particles (unspecific surface action)
- 5 Submicroscopic crystals (specific surface action)

BIOLOGIC ACTION OF ELECTROLYTES AND ITS RELATION TO THE ACTION OF MINERAL WATER

An enormous amount of experimental work has been done on the relation between inorganic ions and healing action. This extends to the electrolytic colloid-chemical action of the salts dissolved in mineral waters. It is an interesting fact that for the optimum of life and its functions a definite ratio of sodium, potassium and calcium is necessary, from sea water to the blood of man this ratio is maintained at 100 : 2 : 2. A fundamental experiment on the significance of dissociated salts, the electrolytes, was made, as is well known, by Jacques Loeb, in which he showed that individual electrolytes were toxic to living organisms. Not only the sodium, calcium, magnesium and iron salts, however, but also the numerous rare electrolytes of the body take part in the metabolic mechanism. We still know too little of the action and significance of the many individual ions. It has been established, however, that the electrolytes play a part in determining the constitution of man, and that in the cooperation of many electrolytes is to be sought one of the fundamental curative factors in the therapeutic use of mineral springs. The use of drinking cures stands preeminent in the possibility that it offers of administering to the human body sufficient quantities of electrolytes in a dissociated state and in combination with many other ions. By means of baths, too, ions such as calcium can be brought through the skin, as Wermel has recently shown. Thus, for example the waters of Franzensbad and Nauheim, the world famous heart baths, contain, besides traces of iron, large quantities of calcium, they are supersaturated with carbonic acid and are also radioactive. The famous American springs at Saratoga are no less valuable, and they were chosen by us for experimental material.

COMPLEX COMPOUNDS AND WERNER'S THEORY

While, as has been briefly stated in the foregoing, we are relatively well orientated, as a result of rich experimental material, with regard to the physiologic action of the simple electrolytes in mineral waters,

² For instance, as has been shown by Miss Marian Irwin, the dyestuff brilliant cresol blue penetrates into the living cells of *Vitella* in the form of the undissociated molecule (J. General Physiol. 9: 561, 1926).

our knowledge of the question of the formation and balneologic action of complex ions has not yet been analyzed. So complicated a salt mixture as natural mineral water, which also contains the complex-forming carbonic, silicic and boric acids, is predestined to form more or less stable complexes. The formation of complex ions stands in intimate relationship not only to resorption and assimilation, but also to the general biologic action of the physiologic metals. Before we go into the question of the existence of complex ferrous compounds in the Saratoga springs, we shall present a brief explanation of Werner's theory,³ which, as is well known, forms the basis of inorganic structural chemistry. Werner's new conceptions of valence and his new interpretation of the stereochemistry of inorganic compounds will undoubtedly prove to be of the greatest value.

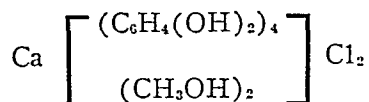
In order to explain Werner's ideas of valence in a few words, we shall choose as an example a typical so-called complex salt, namely, potassium ferrocyanide. In this salt $K_4Fe(CN)_6$, there are present, on one hand, linkages (between iron and cyanide radicles) which, when the salt passes from the crystalline state to the dissolved state, remain unchanged, and, on the other hand, linkages (between $[Fe(CN)_6]$, and the potassium atoms) which are ruptured by the action of the solvent with the formation of potassium ions and ferrocyanide ions $Fe(CN)_6$ which undergo ionic migration as distinct individuals. These ions can recombine spontaneously with the restoration of the $K_4Fe(CN)_6$ lattice. We thus establish the existence of two types of linkage which differ markedly in their behavior. One type resists the change in state on going into solution, while the other type on going from the solid state into aqueous solution is broken down by the solvent, with the result that the individual ions from the ionic lattice come into evidence.

STRUCTURE OF INORGANIC COMPOUNDS AND THEIR RELATION TO BIOLOGIC PROCESSES

Since the introduction of the classic dissociation theory (1886), the biologic interest in ordinary inorganic salts has generally been limited to the action of the simple ions which are formed in solution. This limited point of view involves only the principal valencies and neglects entirely the auxiliary valencies which are exerted in the formation of complex compounds to which great biologic significance must be attached. In calcium chloride, for example, calcium and chlorine are joined by so-called principal valencies. Besides the principal valencies, however, the calcium possesses six auxiliary valencies, which are able to link atoms, molecules, groups or radicles, the calcium itself forming the

3 Werner, A. *Neuere Anschauungen auf dem Gebiete der anorganischen Chemie*, Aufl. 4

coordination center Thus, to give only one example, the calcium in calcium chloride (CaCl_2) can still link coordinately four pyrocatechol and two methyl alcohol molecules, with the formation of the following complex salt



A complex calcium phosphate forms the principal constituent of the mineral substance of bones and teeth It has been shown only recently that the widely occurring mineral apatite $[\text{CaCO}_3 \cdot 3\text{Ca}_3(\text{PO}_4)_2]$ is identical with the calcium phosphate complex in the bones, not only in its chemical composition, but also in its submicroscopic structure (crystal architecture) In most mineral waters we find calcium carbonate besides small amounts of calcium phosphate, silicic acid and boric acid We cannot consider mineral water, which contains so complex a mixture of salts, simply as a mosaic of the individual constituents, but must keep the idea before us that even liquids have a definite structure, in a certain sense, that is to say, affinities come into play between the substances in a solution and the water molecules thereof whereby inorganic molecules of definite structure are created Water plants or sea animals are adapted to the structure of the liquid surrounding them in an exceedingly sensitive manner In biologic fluids, moreover, the correlation between the dissolved substances is of greatest significance They stand to each other in demonstrable physico-chemical relationships, from which it results that the resorption of a substance from a solution is different, depending on whether it is present alone in solution or in company with others Foods, too, act reciprocally, that is to say, each contributes to the assimilation of the other Therefore, substances which are present only in small amounts become of the greatest importance because of these affinities, that is, by means of the formation of more or less stable complexes Thus, for example, Spiro⁴ has shown that the boric acid occurring in the water of Baden (Switzerland) is easily resorbed, because it is of itself lipoid-soluble and readily forms complexes the physiologic behavior of which deserves special attention

We see from these examples that the physiologic action of a mineral spring cannot be judged from its chemical analysis The recognition of this fact, however, does not by any means exhaust the biologic variability of a salt mixture Fresh mineral water is crystal clear, in contact with air, however, a precipitate of originally dissolved material sooner or later separates from it Well known examples are the precipitation of aragonite from the hot Carlsbad springs and of iron

⁴ Spiro Schweiz med Wchnschr 45 1021, 1926

compounds from non-containing springs. We speak, in general, of the aging of a spring. Saratoga water, for example, becomes opalescent in contact with air in the course of minutes, and thereby loses important catalytic properties concerning which we shall report in detail later.

It is seen that by the contact with air and with the escape of carbon dioxide and other gases from the clear solution, a solid substance separates itself from the water. It is only in exceptional cases that nature produces a solid substance without at the same time giving it a specific form, a structure, which on its own part influences the chemical behavior of the substance. Consequently, we must direct our attention toward the formation (building up of the structure) of a solid substance as a result of its origination and transformation processes, as well as toward the mechanism by which its form serves in the course of chemical processes.

A definite process of formation leads to a definite structure, and the physiologic action of an inorganic salt depends, as we have found, much more on its constitution (inorganic structure) than on its chemical composition. Thus, one and the same substance (Fe_2O_3) in forms of different structures appears to act like two different chemical individuals.⁵ In the formation of colloidal precipitates there are two factors, designated by Haber as arrangement and heaping velocities, which play an important rôle. These are not of invariable magnitude, but depend on the nature of the substance and on the external conditions. If we apply these relationships to the mineral water question, for example, to a spring that contains large amounts of dissolved calcium carbonate, then it will depend on the conditions mentioned whether or not the labile μ calcium carbonate first separates out and then goes over into the more stable form (aragonite). Although both carbonates have the same chemical composition, it is justifiable to assume, on the basis of the investigations of Welo and Baudisch, Webster and Baudisch, and of Bickel and his co-workers, that the physiologic action of the two can be different, depending on whether the one or the other is required for assimilation. This is true, first, because of the different solubilities and the closely related resorption and assimilation of the two substances, second, in consequence of the difference in the topography of the crystal surfaces and the closely related development of catalytically active atomic heaps (Taylor) or activated atoms, and third, in consequence of their different energy contents. Just as amorphous carbon, diamond and graphite have different energy contents which manifest themselves in the heat of combustion of these substances, so also must μ calcium carbonate (hexagonal), aragonite (rhombic), and calcite (rhombohedral) possess different energy con-

⁵ Welo, L. A., and Baudisch, O. Science **52** 311, 1925.

tents In the one case, graphite presents the form which contains the least energy and is most stable, and in the other case it is calcite It must be particularly noted here, not only that the three calcium carbonates evidence macroscopic crystallographic differences, but also that, according to Wyckoff,⁶ the atoms of these substances possess different spatial arrangements and therefore different roentgen-ray spectrograms Such facts seem to point out that in the modern investigation of the physiologic action of mineral springs and of inorganic salt mixtures in general, roentgen-ray spectroscopy is a new and not to be underestimated tool By means of our roentgen-ray spectroscopic investigation of the so-called active and inactive iron oxides and their use as biologic catalyzers, the fact has been brought out that we must also consider the action of mineral salts biodynamically In general, undoubtedly, the specific structure of inorganic salts and their changes in structure are bound up with life processes just as closely as is the structure of organic compounds

In connection with the influence of light on simple inorganic compounds, we shall again speak of the Werner conception of valence, first setting down the following principles We differentiate between electrovalence and coordination valence In the former, we conceive that electrons of the outermost shell are transferred to the corresponding shell of another element These are the valence electrons, and the forces involved are electrostatic—that is, we are dealing simply with the transfer of negative electricity In coordination valence we know for a certainty today that not only purely electrostatic forces come into play, at least in the transition elements The binding electrons which unite various radicles with a central atom do not lie on the outermost shell, but may come from deeper lying shells Thus it happens that metallic atoms such as cobalt and nickel, which are similar with respect to their valence electrons and, therefore, with regard to their ordinary ionic reactions, have completely different properties in certain complex ions The radicles bound to the central atom can often change the electronic architecture of the central atom most strikingly⁷

DETERMINATION OF THE CATALYTIC ACTIVITY OF FRESH AND BOTTLED SARATOGA WATERS

In connection with the foregoing, we have been particularly interested in the catalase action of the pentacyano iron compounds As will be seen from chart 1, the hydrogen ion concentration strikingly influences catalase action Besides this catalase action, ordinary iron

⁶ Wyckoff *Am J Sc* **10** 325, 1925, *Ztschr f Kryst* **61** 525, 1925 Rinne, *Γ ibid* **60** 55, 1924 Heide, *F Centralbl f Min*, 1924, p 641

⁷ Welo and Baudisch *Valence Theories and Magnetic Properties of Complex Salts*, *Nature* **116** 606, 1925

salts, and particularly certain complex iron salts, possess a strong peroxidase action. In order readily to demonstrate this peroxidase action we employed the benzidine hydrochloride—hydrogen peroxide (blue), the toluidine—hydrogen peroxide (green), the guaiac resin—hydrogen peroxide (dark blue), or the phenolphthalein (pink) color reactions. To detect ferrous iron, we used the ammonium salt of orthonitrosophenol,⁸ which gives a beautiful green color with divalent iron even in great dilution. Fresh Saratoga water gives all these color reactions brilliantly. Our attention and interest in mineral water was directed first toward its catalytic activity, and in the experimental part of this article are presented the results of a study of the catalytic activity of the Saratoga springs.

We have considered it necessary to give a thorough theoretical introduction, since we wish to demonstrate to the progressive thinking medical world and to the cultured laity that the whole armor of the modern valence theory and electron theory is required to understand that a new epoch in mineral water therapy is at hand—not only in mineral water therapy, but also in mineral metabolism. It is not, as was formerly believed, the ash analysis which informs us as to the assimilatory value and significance of the physiologic metals, but rather the structure of their salts in the living protoplasm. The structure, however, varies with the environmental air, light, climate, season, geologic nature of the soil, soil bacteria, composition and structure of the spring water, nutrition and other factors. Up to the present, investigations of the physiologic action of inorganic salts have been chiefly concerned with the action of the simple ions, potassium sodium, calcium sulphate, and chlorine, while no attention has been paid to their reciprocal action and to the formation of complex ions. In studying the action of mineral water, we must pay particular attention to this interaction and to the formation of complexes, since we are dealing with a complicated salt mixture. In this connection we can best compare mineral water with sea water to which, as we have already noted, inhabiting plants and animals are most delicately adapted. This adaptation, however, not only runs parallel with the chemical composition of sea water, but also harmonizes completely with the varying physical conditions (pressure, light, oxygen supply and other factors) which are met in the depths. It may be assumed, therefore, that mineral water, too, which is under enormous gas pressure, will have biologic properties different from those of surface water. It is our hypothesis that mineral water suddenly forced to the surface may retain its distinctive physicochemical properties for a short time. This can explain the special activity of water at the spring in contrast to aged water—a fact

⁸ Baudisch, Oskar and Karzeff, Nikolaus. *Ber d deutsch chem Gesellsch* 45 1164, 1912.

which has been known for a long time. Methods are still lacking for demonstrating chemically or physically this short-lived condition of a mineral water, yet the researches made by Haeitl on water taken at great depths by means of his new deep-sampling apparatus without diminution in gas pressure, give promise of results in this direction. We, therefore, hold to our former idea⁹ that the water coming from great depths may possess particular properties which it loses at atmospheric pressure. The foregoing conception does not contradict the recent publication of Fresenius¹⁰ on artificial mineral waters and the direct imitation of natural springs.

Our own experiments with Saratoga water indicate that the ability of a water to maintain its activity in bottles depends to a great extent on the depth from which the water is drawn and on the geologic strata from which it comes. The mere fact that, in a certain sense, mineral

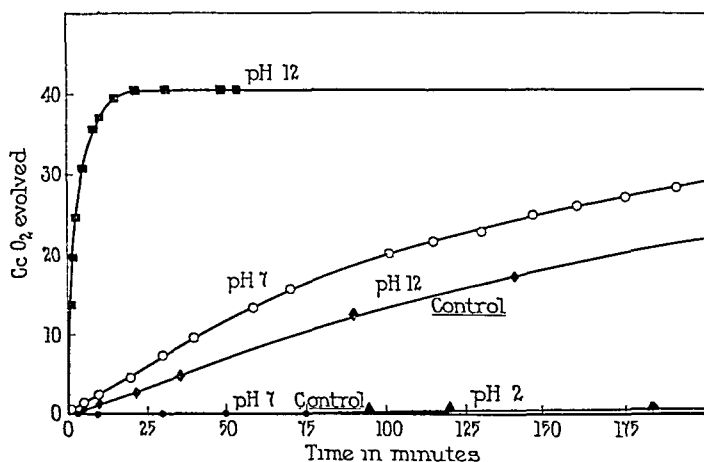


Chart 1—The results of experiments on the catalase action of sodium aminopentacyano ferroate, $\text{Na}_5\text{Fe}(\text{CN})_5\text{NH}_2$. In each case 10 cc of 0.356 molar hydrogen peroxide was combined with 0.1 millimol of the iron salt and the evolution of oxygen followed as described by Baudisch and Davidson. *J Biol Chem* **71** 501, 1927.

waters possess a structure of which its action is a function, shows that we cannot make any generalizations regarding physicochemical and biologic properties of mineral waters of a different locality. The influence of depth and the significance of radioactive substances in the catalytic and biologic properties of mineral waters forms, however, another study, and will not be dealt with further in this paper.

With regard to the chemical and physical nature of the solid precipitated constituents of mineral waters, previous investigators have indicated only its colloidal nature and have quantitatively related the

⁹ Baudisch, O., and Welo, L. *Naturwissenschaften*, Berlin **13** 755, 1925.

¹⁰ Fresenius, L., Eickler, A., and Lederer, H. *Ztschr anorg Chemie* **160** 273, 1927.

size of particle with catalytic activity We state, on the contrary, that on the basis of the analogies mentioned, the structure of the precipitated submicroscopic crystals must be of the greatest importance In the calcium carbonate and iron oxide examples we have noted that in one and the same compound it is possible to obtain different lattice arrangements of the atoms in the molecule and, thereby, substances with surfaces of different catalytic activity We shall go still further and show that even with the same lattice arrangement different substances can be obtained when, as a result of the method of formation, one substance has a perfect lattice while the other lattice structure is not completely developed so that strains in the crystal ensue In the case of charcoal, Ruff has introduced the concept of active and inactive carbon The former contains atoms which are not members of the lattice structure, and which bring about the occurrence of so-called residual affinity If, therefore, we desire to produce crystals with active surfaces, we must direct the empirical preparative methods toward obtaining an incomplete lattice structure or loosening a perfect one

It is clearly demonstrated, then, that the concept of activity must be connected not only with the size of the crystal, but also with the quality of its development Our researches on iron oxides have led us to similar results With the ferromagnetic magnetites, hysteresis measurements are sufficient to demonstrate directly that crystals which are formed quickly and which have no time to grow manifest an internal strain which disappears on heating to red heat The reactivity of such a strained magnetite, and of the "active" iron oxide derived from it, is considerably greater than that of an unstrained sample in which crystals were formed slowly

We have discussed the simple iron compounds studied by Baudisch and Welo¹¹ at some length in order to develop and explain the principal theme of this work, namely, the significance of the structure of simple inorganic compounds in relation to their biologic action While our previous knowledge of iron and aluminum hydrates has been limited to molecules containing one atom of the metal [$\text{Fe}(\text{OH})_3$ and $\text{Al}(\text{OH})_3$], the recent investigations of Willstatter¹² show that aluminum forms hydrates in which several atoms of the metal are bound together by oxygen bridges The selectivity of these structurally different aluminum hydrates is a most baffling phenomenon

It is interesting that among the iron minerals, several hydrates are found in which the composition is identical $2\text{Fe}_2\text{O}_3 \cdot 3\text{H}_2\text{O}$ (xanthosiderite, limonite and other minerals), but in which the chemical and physical properties are different There is a new and fertile field of

11 Welo, L. A., and Baudisch, O. *Philosoph Mag* **50** 399 1925 **3** 396 1927

12 Willstatter *Ber* **57** 58, 1924

work for the biochemist in the study of structural differences of inorganic compounds by biologic methods. Such a study would be the basis for the scientific investigation of the therapeutic action of mineral springs. The answer to the question—Can a fresh natural mineral water be artificially reproduced?—is thus self-evident. Only the most exact biologic methods can convince us that our experimental efforts in this direction have succeeded.

In conclusion, we may say that the present state of scientific mineral watertherapy is analogous to that in which the science of fermentation found itself fifty years ago.

Many and varied processes of fermentation became known during the centuries chiefly as a result of empirically established principles which, however, were supported by the observations of outstanding and critical observers. When, however, the cause of fermentation was found to be an organism of one cell and all the knowledge of chemistry, physics, physiology and other sciences began to be utilized, it was possible to put many of the empiric observations on a scientific basis. In this way control was gained over certain biologic processes which previously had to be left to chance.

But here, just as in bacteriology (in which it was originally thought that bacteria alone are sufficient to cause disease), there were disillusionments. While the splitting of sugar was at first ascribed to the metabolism of a single cell organism, the researches of Buchner overthrew this apparently well established fact and made the activity of enzymes known. Recently, however, the great significance of the unimpaired living cell structure in quantitative fermentation has been demonstrated.

The concept that the structure of a reacting substance is of significance is penetrating further and further into biology. In the present work, we have developed the new idea that the structure, and not alone the chemical composition of simple inorganic salts, is important in the course of certain biologic processes.¹³

A systematic study in this direction should be just as fruitful for the problem of mineral springs as the discovery of the cause of fermentation was to that science. The action of mineral water is not merely due to the effect of a complex salt solution, for we know that we must also consider the source of the spring—one might almost say the geology and mineralogy of the spring—in order to understand completely its therapeutic action.

¹³ Webster and Baudisch. *J. Exper. Med.* **41** 473, 1925. Kohlschutter, Von Die Form des Stoffe im chemischen Vorgang. *Naturwissenschaften*, Berlin **11** 865, 1923.

EXPERIMENTAL WORK

Qualitative Investigations—For our research the most accessible springs were those of Saratoga in the state of New York. Saratoga possesses numerous springs, but the present investigation has been limited to those known as Geyser, Coesa and Hathorn No 2. Before describing our experiments, we shall give a brief sketch of the geology of the Saratoga district.

The general geologic condition existing over the whole Saratoga triangle, which takes in a territory about 4 miles square, is as follows: drift, gravel, clay, shale, siliceous limestone, dolomite strata and sandstone. The thicknesses of these various strata are slightly different in the different localities, and at times we find duplications of the strata, due to the upheaval of the west side of the fault.

TABLE 1—*Chemical Analyses of Mineral Waters at Saratoga Springs, N. Y.**

Chemical Combinations	Hathorn No 2	Coesa	Geyser
Ammonium chloride	76.49	28.68	45.88
Lithium chloride	75.59	44.27	24.22
Potassium chloride	896.28	506.07	260.77
Sodium chloride	10,569.88	5,558.32	2,387.19
Potassium bromide	72.00	20.00	16.00
Potassium iodide	2.80	2.40	.80
Sodium sulphate	Trace	Trace	Trace
Sodium metaborate	Trace	Trace	Trace
Sodium nitrate	Trace	Trace	Trace
Sodium nitrite	Trace	Trace	Trace
Sodium bicarbonate	1,294.85	614.48	2,047.79
Calcium bicarbonate	3,721.64	2,508.06	1,718.65
Barium bicarbonate	38.88	34.31	16.88
Strontium bicarbonate	Trace	Trace	Trace
Ferrous bicarbonate	14.27	19.62	14.27
Magnesium bicarbonate	2,720.27	1,631.42	851.72
Alumina	23.59	3.19	1.59
Silica	9.80	9.80	13.40
Total	19,516.34	10,980.62	7,399.16

* Made by Reservation Chemists for the State Reservation at Saratoga Springs.

* The results of the analyses are expressed in milligrams per liter. The waters of all the springs are at normal atmospheric temperature and pressure, supersaturated with carbonic acid gas.

At the Coesa spring, we find no drift, gravel or clay, the rock is practically on the surface in this neighborhood, as there are about 9 feet of casing in the seal. The well itself is drilled to a depth of 420 feet. There is a seal in the well at 376 feet, at which point the water is taken in a quantity of about 15 gallons a minute.

The Geyser spring has but little casing in it, the depth of this is unknown, as we have no record giving us these particular data, but the rock at this point is also close to the surface. This surface rock is composed of shale, both in the Geyser district and in the Coesa district. The Geyser spring is bored to a total depth of 144 feet, the seal is at 131 feet, from which point the water is taken in a quantity of about 3 quarts a minute.

All of the waters of Saratoga Springs are found in the dolomite strata. In the case of the Geyser spring, the dolomite is found just under the shale, while in the Coesa spring there are several layers of siliceous limestone superimposed on the dolomite strata. It has been found to be a general experience in Saratoga that wherever most of the bore is located through shale rock, the waters are high in bicarbonate of soda, and that wherever less shale is present and the greater part of the depth of the bore is located in limestone, the waters are more saline and contain more carbonate of lime and magnesia and less bicarbonate of soda.

Catalytic Activity of the Geyser Spring—This spring is most interesting to us because we had the opportunity to compare the catalytic activity of fresh water from it with that of water that had been stored in white bottles for seven years. In our former paper entitled "On the Aging of Natural Mineral Water,"¹⁴ we remarked that aged waters differ from the fresh in a loss of catalytic activity. We have further reported that light promotes aging. These observations were the result of rather crude experiments carried out at the Glauber springs of Franzensbad. These results, however, still stand today, and Heubner,¹⁵ who has carried out analogous experiments on the Pyrmont iron springs, arrived at similar results. Since the earliest investigations of the destructive action of mineral waters on hydrogen peroxide the statement has repeatedly appeared that this property is noted only in fresh waters. We were, therefore, much astonished to find that Geyser water which had been stored for seven years in colorless bottles without any particular protection from the light still showed a strong peroxidase or catalase activity. It is noteworthy that in the course of years no precipitate formed in these bottles as is usually the case in old mineral water. The clear contents gave all the previously mentioned peroxidase color reactions intensely and showed a brilliant green color with orthonitrosophenol, which indicated the presence of ferrous iron. It was striking that the water taken directly from the spring did not react so intensely as the water which had aged several years. Acidified potassium ferricyanide failed to indicate the presence of ferrous iron. In the absence of air the solution remained unchanged, and only in an open tube did the color change on standing from yellow to light blue. An artificial ferrous bicarbonate solution of like iron content (0.0260 Gm per liter) gave an immediate pale blue with potassium ferricyanide. If Geyser water is irradiated for a short time in the presence of traces of oxygen, it gives an immediate blue with acidified ferricyanide. While orthonitrosophenol is capable of indicating the ferrous iron of the catalytically

14 Baudisch, O., and Welo, L. A. J. Biol. Chem. **64** 753, 1925

15 Heubner. Ztschr. f. Wissensch. Baderkunde **1** 74, 1926

active Geyser water in that it forms a green colored complex ferrous orthonitrosophenol, no Prussian blue is formed by ferricyanide in the absence of oxygen. By means of these color reactions, it was primarily established that an aged mineral water does not necessarily lose its peroxidase property, the opposite has previously been taken to be the fact.

There was a high pressure of carbon dioxide in the old Geyser water bottles, and it might have been assumed that the catalytic power was related to the dissolved carbon dioxide. Mineral water was therefore placed in a suitable separatory funnel with a neck 20 cm long and 3 cm wide, air being excluded. The water was covered with white petrolatum to a height of several centimeters. The excess of carbon dioxide escaped through the petrolatum which was maintained in liquid state, and completely shut out oxygen. In twelve hours the bubbling of gas ceased. The water in the funnel was still clear and gave all the peroxidase color reactions just as intensely as the original carbon dioxide containing water. The contents of the funnel were then heated nearly to boiling. Under these conditions, the water became cloudy due to the decomposition of bicarbonates. The funnel was allowed to stand for five days, during which time a gradual precipitation of solid constituents began. The surface remained continuously covered with petrolatum, however, while the stopcock of the funnel was kept under alkaline pyrogallol solution. When tests were then made with benzidine hydrochloride—hydrogen peroxide, the color reaction was blue, with phenolphthalein, deep red, with guaiac resin, deep blue and with orthonitrosophenol, brilliant green.

This experiment brought the fact that neither the dissolved nor the bicarbonate carbon dioxide was necessary for the color reactions.

EFFECT OF LIGHT ON MINERAL WATER AND FERROUS BICARBONATE SOLUTIONS

Three parallel light experiments were now undertaken, which immediately gave the clue to the explanation of the loss of catalytic reactions previously observed. Three quartz test tubes which had been drawn out to capillaries at the upper end were employed. Two of these were filled about three-fourths full (*A* and *A'*), while the third (*B*) was completely filled in the absence of air so that the liquid reached to the capillary. The three tubes were then sealed off in the oxyhydrogen blowpipe. *A* and *A'* had not been rinsed with carbon dioxide as had *B*. *A* and *B* were then irradiated with a carbon arc light for nearly two hours while being cooled with running water at 13 C. At the end of this time the contents of the tubes were slightly opalescent. Tests of the two tubes gave entirely different results. In *A* all the peroxidase reactions had disappeared, and orthonitrosophenol gave a reddish color

instead of the green, indicating that ferric iron was present. The opalescent contents of *B* gave all the peroxidase reactions intensely as well as a green color with orthonitrosophenol. The contents of *A'*, which had been kept in a dark incubator during this time, were only slightly opalescent, while all the color reactions were considerably weaker than originally. *A* and *A'*, which contained traces of oxygen, differed extraordinarily after the irradiation, although more of the excess of carbon dioxide could escape and considerable pressure of carbon dioxide was present in the tubes. Light, then, effected the complete oxidation of the ferrous iron in the tube which contained oxygen, whereupon all the peroxidase reactions disappeared.

Although *A'* had been subjected to a higher temperature than its irradiated duplicate, it retained its catalytic properties to some extent. The oxidizing power of oxygen is enhanced by light energy, as can better be seen from the quantitative experiments to be described. In *B*, in which no trace of oxygen was present, the catalytic properties were completely retained, although a visible opalescence occurred. This signifies an increase in the size of the particles which originally were not even visible by the Tyndall phenomenon.

These qualitative experiments established the fact that the short wave lengths of the light of the carbon arc, to which quartz is transparent, exert an influence on Geyser water in the absence as well as in the presence of oxygen. In the absence of oxygen no oxidation of the ferrous iron occurs, and, therefore, no decomposition of water. As further evidence of this fact, a solution of ferrous pyrocatechol was prepared. In the absence of oxygen this solution is colorless. Irradiation for one hour with the carbon arc did not cause the least apparent change. If, however, a small amount of potassium nitrate were added and the solution again irradiated, an intense violet color occurred in a few minutes. Ferric pyrocatechol, which is similar to permanganate in color, was formed by the oxygen split off from the nitrate.

We have already indicated in the described experiments with potassium ferricyanide that the ferrous iron in Geyser water does not always behave like that in ferrous bicarbonate. It was therefore of interest to study the behavior of a solution of ferrous bicarbonate on irradiation. For this purpose a ferrous bicarbonate solution containing 0.178 Gm. of ferrous iron per liter was prepared. When this solution was irradiated while being cooled in running water, it soon developed a yellowish clouding, and finally a precipitate settled out which was reddish brown and consisted of ferric carbonate. After an hour's irradiation, the water still contained 0.05584 Gm. of ferrous iron per liter.

This experiment indicates that ordinary ferrous bicarbonate solutions are sensitive to light, decomposing water with the formation of

hydrogen, while the ferrous salt is oxidized to ferric carbonate. In this case, therefore, the iron ion in ordinary ferrous bicarbonate behaves differently from the complex ferrous ion in mineral water. A solution of ferrous bicarbonate prepared from the purest iron (from iron carbonyl), water and carbon dioxide, containing 25 mg of iron per liter (as does the Geyser water) gives the reactions with benzidine, toluidine, guaiac resin and orthonitrosophenol just as strongly as does Geyser water, but it gives no reaction with phenolphthalein, though all the catalytically active springs which we have investigated give, in the presence of air (but without hydrogen peroxide), a precipitate of zinc carbonate which is at first rose-colored and which quickly becomes intense red. If, however, the divalent iron in mineral water is transformed into the ferric form by means of traces of air and intense irradiation, then only the flocculent white precipitate of zinc carbonate and no red color, occurs. This indicates that the red coloration depends on the presence of active divalent iron and not on the other inorganic salts. It is this element alone which is capable of quickly absorbing and activating atmospheric oxygen so that the colorless phenolphthalein becomes oxidized to phenolphthalein which, in the alkaline solution, forms its familiar red potassium salt. Neither dilute nor concentrated ferrous bicarbonate solutions give a red color with phenolphthalein (with or without hydrogen peroxide). In the absence of peroxide, the concentrated solution gives a green precipitate of ferrous hydroxide while in the presence of hydrogen peroxide all the iron is instantly converted to the yellowish-red ferric hydroxide without the phenolphthalein.

Phenolphthalein mixed with H_2O_2 forms the well known blood reagent of Kastle and Meyer,¹⁶ which is sensitive to blood as dilute as 1:800,000. This reagent is of particular interest in connection with the catalytic properties of mineral waters, since in them the red coloration occurs in the absence of H_2O_2 and also because oxygen or air is necessary besides divalent iron. As long as the mineral waters investigated gave a green color with orthonitrosophenol (Fe^{II}) a red color was obtainable with phenolphthalein, whether the water contained an excess of carbon dioxide or was heated nearly to boiling.

Quantitative Investigations of Geyser Spring—The method of investigation of the catalase action of mineral water was developed by Glénard.¹⁷ The following is the method as employed by us

16 Glaister, John. Brit. M. J. 1:650, 1926. Preparation, phenolphthalein (2 Gm.), potassium hydroxide (20 Gm.), and water to make 100 cc. are boiled while zinc dust (from 10 to 30 Gm.) is added until the solution is decolorized after boiling ten minutes. The solution keeps well if a little zinc is present.

17 Glénard. Propriétés physicochimiques des eaux de Vichy, Paris, 1911.

Two hundred cubic centimeters of mineral water or the solution to be investigated was quickly brought to 37 C by immersion in a hot water bath and mixed with 25 cc of approximately half molar peroxide (at 37 C). The peroxide was freshly prepared by diluting Merck's perhydrol. The time of mixing was noted and the solution then maintained at 37 C in the incubator. After fifteen minutes, 25 cc of the mixture was pipetted out, acidified with sulphuric acid and titrated with tenth normal potassium permanganate. The titration was repeated at definite intervals. The initial hydrogen peroxide (H₂O₂) concentration in the mixture was determined by means of a control with distilled water. Table 2 and charts 2 and 3 which show the extent and rate of peroxide decomposition by Geyser water yield quantitative confirmation of the qualitative color reactions. In our case, peroxidase and catalase reactions seem to run parallel.

TABLE 2—*Catalytic Properties of the Geyser Spring Water*

Time (Minutes) After the Beginning of the Experiment	Cc Tenth Normal Potassium Permanganate	a-x	a	$-\log \frac{1}{t} \frac{1}{a-x}$
			$\frac{a}{a-x}$	
(I) 0	29.35			
15		19.9	1.473	0.0113
45		7.9	2.520	0.0134
90		4.6	1.717	0.0047
121		3.2	1.437	0.0051
(II) 0	30.65			
17		24.70	1.242	0.0056
32		19.52	1.264	0.0068
62		10.88	1.795	0.0085
91		6.75	1.610	0.0071
121		4.80	1.406	0.0049
(III) 0	29.13			
14		22.7	1.285	0.0078
31		15.7	1.447	0.0094
60		6.9	2.28	0.0123
91		4.2	1.64	0.0069
121		3.2	1.31	0.0039
(IV) 0	32.5			
15		30.9	1.051	0.0014
30		28.5	1.087	0.0024
45		24.7	1.153	0.0041
75		16.6	1.481	0.0057
105		8.8	1.886	0.0092
165		4.6	1.913	0.0047

A comparison of our results with the data on European springs brings out a striking difference in both the extent and the velocity of peroxide decomposition. The Geyser spring and, as we shall show later, the other springs, are extraordinarily active. Our observation that water stored in bottles for seven years retains all of its activity is novel, yet it is easily explained in view of other results of our investigation. Geyser water is drawn from pipes over 100 feet deep and is bottled in the complete absence of air, the bottles being preliminarily subjected to careful rinsing with air-free carbon dioxide. The secret of the preservability of the water lies in the ingenious machine which maintains it free from oxygen until it is bottled. The smallest trace of oxygen would, during long storage, gradually oxidize the complex ferrous iron

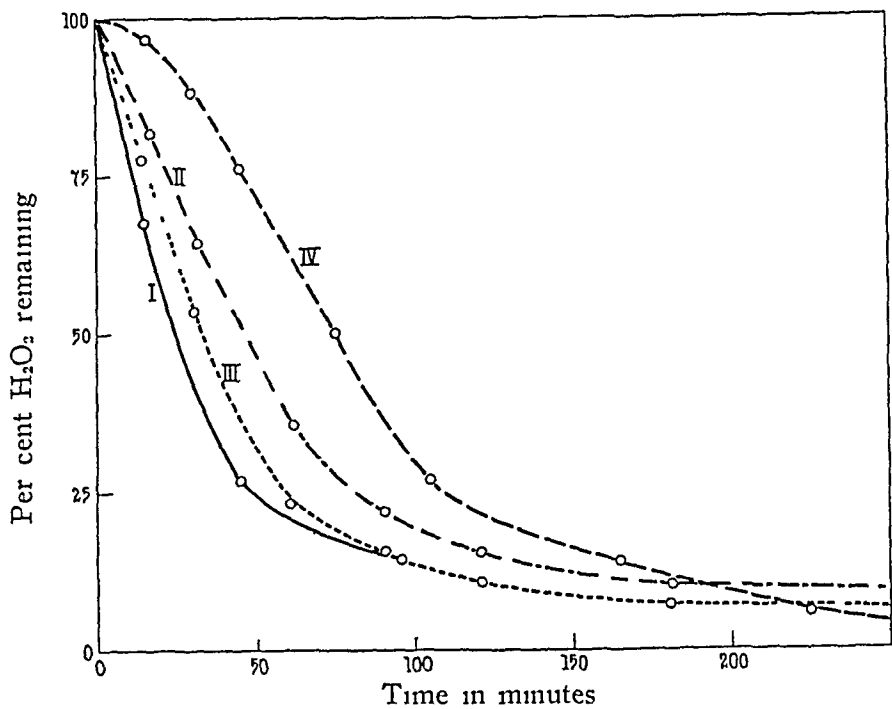


Chart 2—The catalytic properties of the Geyser Spring (fresh and 7 year old water) Curve I indicates Geyser water from bottles filled on Jan 3, 1920, and heated to 85 c in the absence of air, curve II, Geyser water from bottles filled Jan 3, 1920, with the carbon dioxide shaken out before measurement, curve III, Geyser water from bottles filled on Jan 3, 1920, and Curve IV, Geyser water measured at the spring on Jan 2, 1927

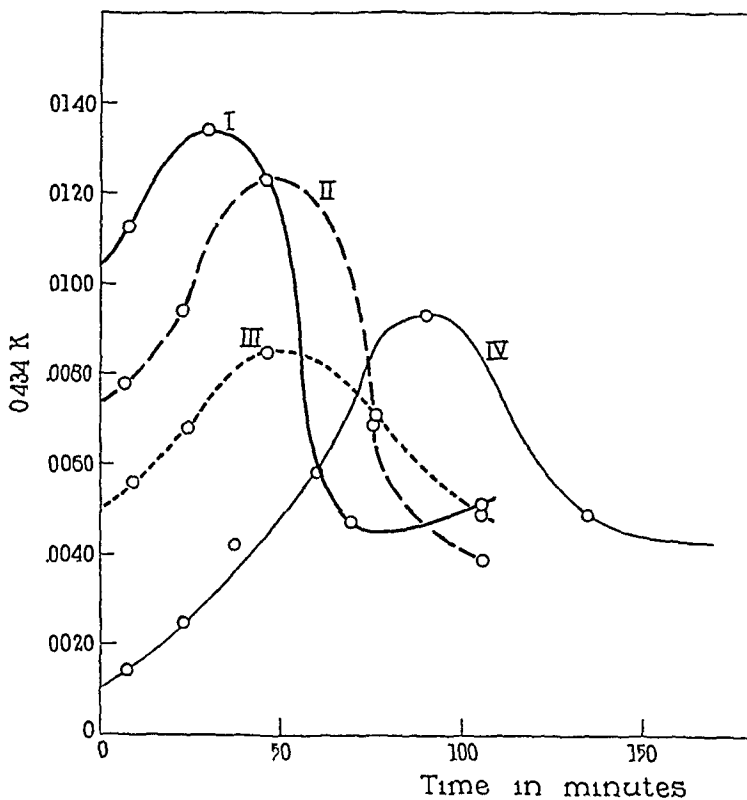


Chart 3—The catalytic properties of the Geyser Spring (fresh and 7 year old water) Curve I indicates Geyser water from bottles filled on Jan 3, 1920 and heated to 85 c in the absence of air, curve II, Geyser water from bottles filled on Jan 3, 1920, with the carbon dioxide shaken out before measurement, curve III, Geyser water from bottles filled on Jan 3, 1920, curve IV, Geyser water measured at the spring on Jan 2, 1927

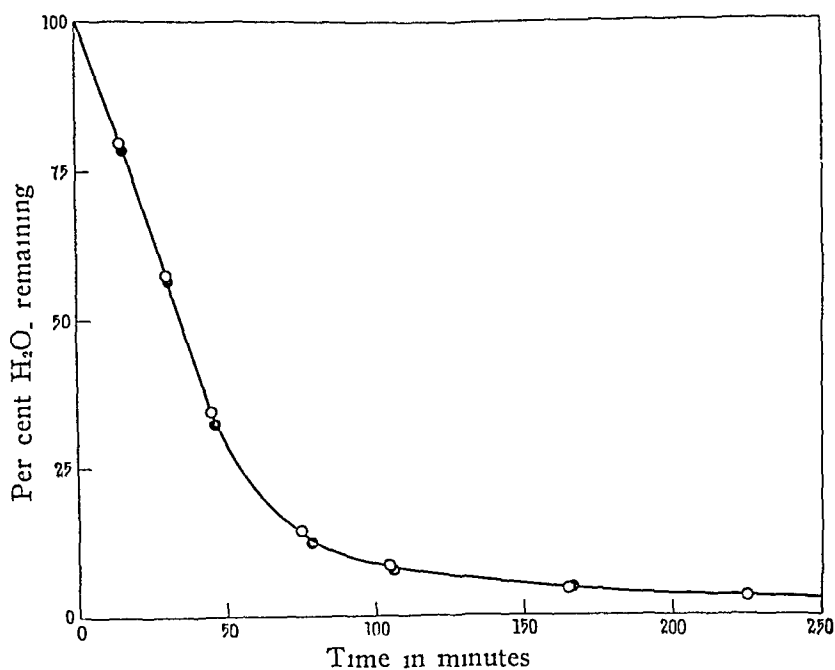


Chart 4—The catalytic properties of Hathorn Spring No 2 The white dot indicates results of water measured at the source on Feb 3, 1927, the black dot indicates results of water bottled Dec 7, 1926

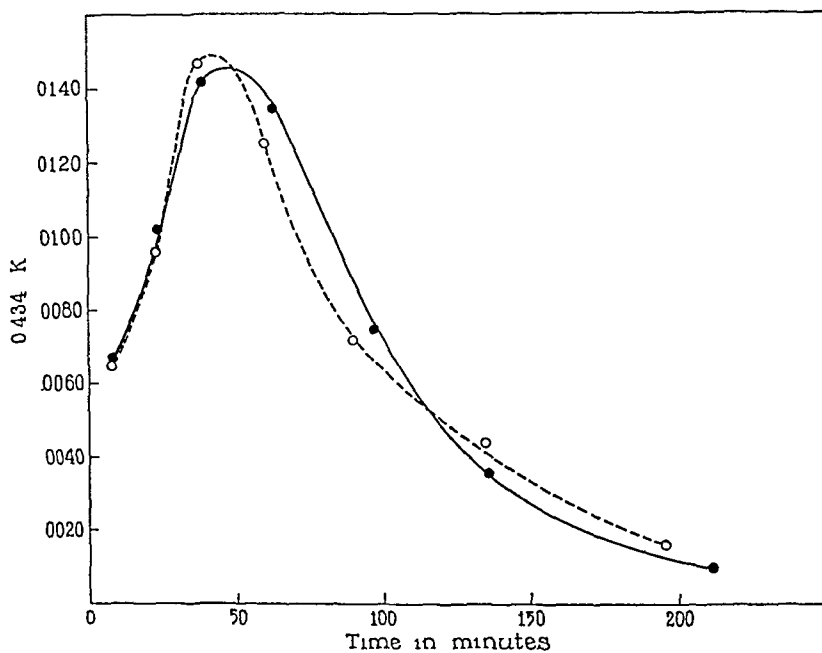


Chart 5—The catalytic properties of the Hathorn Spring No 2 The broken line indicates results of water measured at the source Feb 3, 1927, the unbroken line indicates results of water bottled Dec 7, 1926

to ferric, thereby causing precipitation and loss of catalytic properties. Bottles which show the presence of a precipitate have weak peroxidase-catalase properties or none at all.

It is also seen from our experiments that the catalyst can be precipitated without losing its activity if oxygen is absent. This gives us a splendid demonstration of the fact mentioned previously, namely, that it is not the size of particle but the structure of the solid substance which is important for its catalytic activity. Up to the present it has been assumed that the catalytically active substance in mineral water is molecularly or at least colloiddally dispersed and as a result of this dispersion shows an unspecific surface action.

The Catalytic Activity of Hathorn No. 2 Spring—In charts 4 and 5 is given a representation of the catalytic decomposition of H_2O_2 by

TABLE 3—*The Catalytic Properties of Hathorn No. 2 Water*

	Time (Minutes) After the Beginning of the Experiment	Cc Tenth Normal Potassium Permanganate	$\frac{1}{t} \log \frac{a}{a-x}$		
			$a-x$	a	$a-x$
(I)	0	32.5			
	15		25.9	1.254	0.0065
	30		18.6	1.392	0.0096
	45		11.2	1.660	0.0147
	75		4.7	2.380	0.0125
	105		2.8	1.678	0.0072
	165		1.5	1.866	0.0044
	225		1.2	1.250	0.0016
(II)	0	30.16			
	16		23.6	1.279	0.0067
	30		17.0	1.389	0.0102
	47		9.75	1.743	0.0142
	78		3.72	2.620	0.0135
	106		2.3	1.618	0.0075
	166		1.4	1.643	0.0036
	258		1.14	1.228	0.0010

Hathorn water. It is noteworthy that water three months old had not suffered any loss in catalytic activity. As may be seen from its chemical analysis, Hathorn No. 2 is a highly mineralized water, and in this respect is different from the Geyser spring.

Influence of Light on the Coesa Spring—In connection with the qualitative reactions of the Geyser spring, we have already explained why the carbon arc light sometimes causes an increase or at any rate does not cause a decrease in the catalytic activity of the water, while in other cases the activity is completely lost.

In the study of the action of light on mineral springs, little attention has previously been paid to traces of oxygen. Fresenius¹⁰ says that precipitates are observed in irradiated solutions only when they contain air. He did not observe an influence of light on the catalysts. Schoeller and Rothe¹⁸ do not believe that there is a relation between the

influence of light and the disappearance of catalytic properties of natural mineral water. They assume, further, that the state of the ferrous bicarbonate or rather the presence of the system, $\text{Fe}^{II} + \text{HCO}_3^- + \text{CO}_2$ is responsible for the benzidine reaction and the continuance of the activity. According to their idea, the partial pressure of CO_2 and a lack of oxygen are important for the maintenance of the catalytic activity of a natural curative water. How little all their assumptions harmonize with our experimental results is apparent. That the presence of air diminishes and finally completely destroys the activity of a natural mineral water is a phenomenon which has been known since ancient times.

We have used the carbon arc in our researches because its spectrum approaches most closely that of the sun, and the longer ultraviolet wave

TABLE 4—*The Catalytic Properties of Coesa Water*

Time (Minutes) After the Beginning of the Experiment		Cc Tenth Normal Potassium Permanganate	a—\	$\frac{1}{a-\lambda}$	$\frac{1}{t} \log \frac{1}{a-\lambda}$	p_H
(III)	0	31.2				
	20		29.5	1.058	0.0012	7
	45		25.7	1.149	0.0024	
	75		20.1	1.279	0.0036	
	115		12.6	1.594	0.0023	
	165		5.2	2.422	0.0077	
(IV)	0	31.2				7
	20		30.8	1.013	0.0003	
	45		29.8	1.033	0.0006	
	75		28.6	1.042	0.0006	
	115		26.6	1.074	0.0003	
	165		22.8	1.122	0.0010	

lengths are present in abundance. Preliminary tests showed that the ultraviolet portion of the sun's spectrum was the most effective in our experiments. Later we shall analyze the most active wave lengths in detail.

For our experiments we used Coesa water which had been bottled on Dec. 12, 1926. We had, therefore, a uniform supply of water and could carry out our experiments with all convenience in the laboratories of the Rockefeller Institute, instead of going to the source of the spring. The water gave all the peroxidase color reactions intensely.

Apparatus. The previously described long-necked separatory funnel with a capacity of about 1.5 liter was used. One of these was made of fused quartz and was used for the irradiation experiments. The following parallel experiments, which are best expressed in the charts, were carried out.

Experiments in the Presence of Traces of Oxygen. The contents of four bottles of Coesa water (about 2 liters) were combined in a large beaker from which the water was poured into two separatory funnels, one of glass (A) and

one of quartz (*B*) During this operation the mineral water came in contact with air The water in the funnels was then covered with petrolatum to a height of 4 inches (10.16 cm), which sealed it from the air The funnels were cooled with running water (13 C), *A* remaining in diffused daylight while *B* was irradiated for one hour with the carbon arc light Both funnels were then placed in a dark incubator (37 C) and allowed to remain for three hours At the end of this time, the water in *A* was slightly opalescent while that in *B* was cloudy The p_{H} was 7 in both vessels The results of the measurements of the catalase action are given in table 4

Experiments in the Absence of Oxygen A glass (*C*) and a quartz (*D*) funnel were each filled with the contents of two bottles in the complete absence of air For these experiments the funnels were strongly heated with Bunsen burners to remove occluded gases, while carbon dioxide carefully freed from

TABLE 5—Subsequent Determination of the Catalytic Properties of Coesa Water

	Time (Minutes) After the Beginning of the Experiment	Cc Tenth Normal Potassium Permanganate	$\gamma - \lambda$	$\frac{1}{\gamma - \lambda}$	$\frac{1}{t} \log \frac{\gamma}{\gamma - \lambda}$	p_{H}
				$\gamma - \lambda$	t	
(I)	0	27.8				
	15		24.3	1.142	0.0038	7
	25		21.5	1.150	0.0053	
	45		14.7	1.463	0.0083	
	75		6.8	2.162	0.0112	
	110		2.6	2.613	0.0119	
(II)	0	27.8				
	15		25.8	1.077	0.0021	7
	25		23.9	1.080	0.0033	
	45		19.0	1.258	0.0005	
	75		10.1	1.841	0.0091	
	110		3.5	2.885	0.0131	
(V)	0	26.8				
	15		23.4	1.144	0.0039	
	30		18.9	1.239	0.0062	
	60		10.5	1.750	0.0081	
	100		5.0	2.160	0.0084	
	115		3.9	1.261	0.0071	

oxygen, was passed through them for an hour The funnels were filled while still warm, the vigorous effervescence of the mineral waters hindering the access of air They were then sealed with melted white petrolatum, through which the excess CO_2 easily passed The stopcocks of the funnels were kept under the surface of alkaline pyrogallol solution After forty-eight hours at room temperature, the evolution of carbon dioxide had ceased, both funnels remaining clear *D* was then irradiated for one hour, while being cooled with running water (13 C), when it became distinctly opalescent Both funnels were placed in the incubator for four hours to attain the necessary temperature The p_{H} in both was 7 The results of the subsequent determination of catalytic properties are given in table 5

The experiments in the presence of oxygen only confirm what was previously found by means of peroxidase color reactions in the case of Geyser water Light considerably accelerated the oxidation of ferrous ion Hydrogen ion concentration plays no part in this process because

it, as well as all other conditions, was identical in both cases. Qualitative tests of the water in the two funnels confirmed the result mentioned before. In the unilluminated funnel all the previously mentioned color reactions were positive but weak. The illuminated funnel, on the contrary, did not show any of these reactions, and orthonitrosophenol indicated ferric iron.

The fact that light accelerates the oxidation of ferrous ion by molecular oxygen without at the same time photochemically decomposing water, is of biologic interest. The assumption that in the mentioned

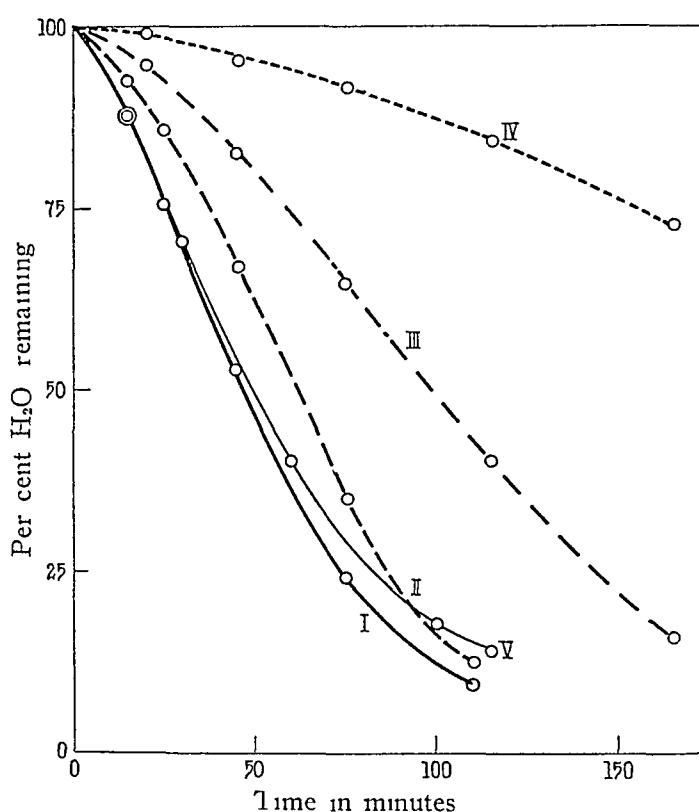


Chart 6—The influence of light on the catalytic properties of Coesa Water (bottled Dec 1926) in the absence and in the presence of oxygen. Curve I indicates oxygen-free water, irradiated, curve II, oxygen-free water, not irradiated, curve III, water with traces of oxygen not irradiated, curve IV, water with traces of oxygen, irradiated, and curve V, water direct from the bottle.

experiments light does not form hydrogen peroxide from water arises from the results of the oxygen-free illuminated experiment (D). If hydrogen peroxide were formed from water by irradiation of mineral water, the ferrous complex would become oxidized, as is the case with ferrous bicarbonate.

The oxygen-free experiment, however, leads to another question which is of fundamental significance for the action of light, namely, the "significance of light for the stability of colloidal solutions." A

large amount of literature already exists on this subject, and this is not the place to discuss it more thoroughly. We are interested only so far as our experimental results are connected with the theme already discussed in the theoretical part of this article, namely, the size and structure of the particle. Up to the present time, the catalytic action of a mineral water has always been related to and explained by the so-called molecularly dispersed or generally colloidal state of the iron or manganese¹⁰. Our experiments with light in oxygen-free water show that light brings about a change in dispersion which finally leads to the pre-

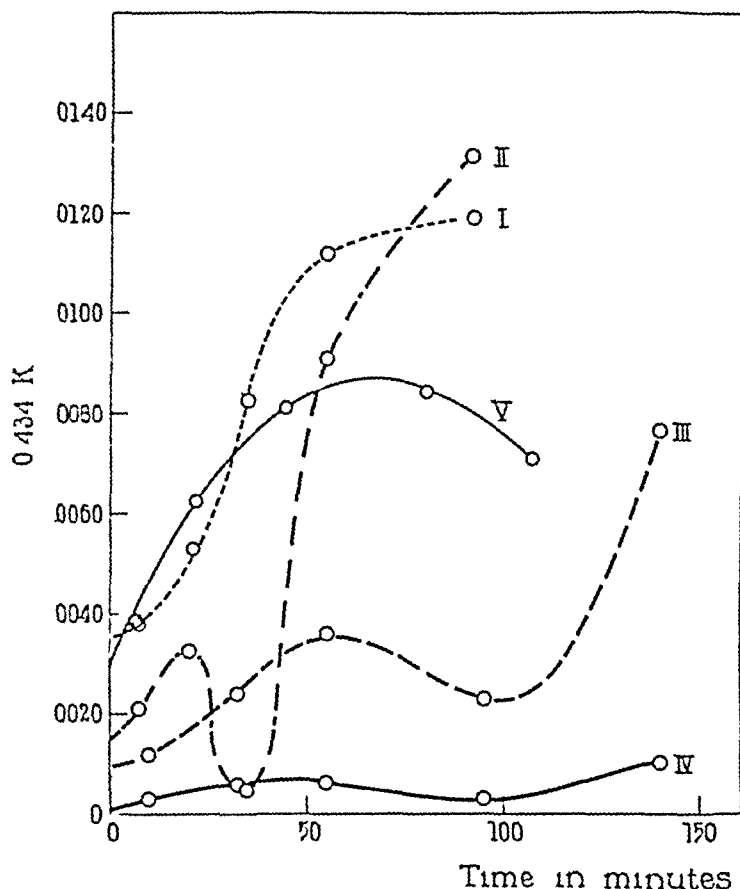


Chart 7—The influence of light on the catalytic properties of Coesa Water (bottled December, 1926) in the absence and in the presence of oxygen. Curve I indicates oxygen-free water, irradiated, curve II, oxygen-free water, not irradiated, curve III, water with traces of oxygen, not irradiated, curve IV, water with traces of oxygen, irradiated, and curve V, water direct from the bottle.

cipitation of the disperse phase (coagulation). Thus, particles which were originally invisible increased in size and became visible under the influence of light. Water was not photochemically decomposed in the process, since such a change would have led to the oxidation of ferrous ion. If the size of the particle alone were responsible for the catalytic activity, the clear unilluminated water should have been more active than the illuminated, which is contrary to the facts. The precipitated particles

of ferrous compound must possess a surface with specially active points since the reaction velocity of hydrogen peroxide decomposition is greater than that with the original molecularly dispersed particles. We see, therefore, that it is justifiable, in the mineral water problem, too, to enlarge on the idea that the process of formation of an inorganic salt is a function of its catalytic surface action.

Even if, on the basis of previous experimental results, we are not able at present, to say definitely that the divalent iron in the Saratoga springs is bound in a structurally defined and isolatable complex salt, it is to be seen that a specific character is contributed to the ferrous ions by their companions in solution, a character which is not dependent on contained gases, particularly carbon dioxide, and which differentiates it from the ferrous ion in ferrous bicarbonate. While ferrous bicarbonate is rapidly oxidized to ferric carbonate by the oxygen resulting from the photochemical decomposition of water, mineral water appears to use the light only for diminishing the charge on its colloidal particles and thereby increasing their mass. To what extent this process can be explained by the change in the dissociation of electrolytes contained in mineral water must be decided by further experiments. It may be said, however, that light influences the dispersion of the colloidal particles in mineral water and thereby its catalytic activity. In the light of modern colloid chemistry, colloidal particles are no longer to be considered simple particles which show unspecific absorption phenomena because of their large surface, but, rather, structurally defined crystals in which the previously mentioned laws of valence find just as important application as in the electrolytes and in the complex salts.

SUMMARY

1 The Saratoga springs investigated by us displayed a much higher catalytic activity than any of the European springs previously investigated.

2 It was observed that bottled waters retain their catalytic activity if every trace of oxygen is excluded in the bottling.

3 The catalytic activity of the Saratoga waters depends primarily on their ferrous iron content, which is most probably in complex form. It is independent of dissolved or bicarbonate carbon dioxide.

4 The mineral waters lose their catalytic activity in the presence of oxygen, especially when irradiated by the carbon arc light.

5 In the absence of oxygen, heat and light alter only the dispersion of the contained colloid particles without weakening the catalytic power.

We wish here to express our thanks to Dr. Herbert Ant, State Chemist at Saratoga Springs, to whom we are indebted for determinations of the catalytic action of the mineral waters at the source, as well as for many helpful suggestions.

MOTION OF THE HEART IN DISEASE OF THE MITRAL VALVE

CINEMATOGRAPHIC ROENTGEN-RAY STUDIES *

W EDWARD CHAMBERLAIN, M D

AND

WILLIAM DOCK, M D

SAN FRANCISCO

Roentgenograms of the heart which do not record the rhythmic movements of its borders must always remain of limited value. Even the orthodiagram, while offering information not to be obtained from the roentgenograms, fails to inform us of the time relations of the movements of various parts of the heart outline.

In 1925, Ruggles¹ succeeded in making 8 by 10 inch instantaneous roentgenograms of the beating heart serially, at the rate of fifteen per second. He reduced these roentgenograms, photographically, on to a motion picture film. When projected Ruggles' film gave an excellent demonstration of the shadow of the moving heart, with detail and visibility far exceeding the best that can be obtained by watching the shadows on the fluorescent screen.

Any one who has observed the movements of the heart, as shown by the fluoroscope or with the greater clarity of Dr. Ruggles' cinematographic demonstration, must appreciate how valuable would be a graphic record of the in and out movements of selected parts of the border of the heart. While watching the demonstration of Ruggles' motion picture, it occurred to us that such a graphic record could be obtained by measuring corresponding dimensions on successive films in any series taken with Ruggles' roentgen cinematograph.

The resulting studies and curves of heart border motion (Skiacardiograms) obtained from Ruggles' original films of a normal subject, have been reported elsewhere.² We have now produced similar records in cases of valvular disease.

In applying this method of analysis of the movements of the heart border to the diseased heart, a number of difficulties were at once encountered. The present apparatus of Ruggles for obtaining the necessary rapid-sequence roentgenograms does not give satisfactory

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1 Ruggles, H. E. X-ray Motion Pictures of the Thorax, Radiology 5: 444 (Nov.) 1925.

2 Chamberlain, W. E., and Dock, W. The Study of the Heart Action with the Roentgen Cinematograph, Radiology 7: 185 (Sept.) 1925.

films of thick-chested patients, and it cannot be used with nervous or bedridden patients. By using high voltage, the value of which has been demonstrated by Lomon and Commandon,³ and by enclosing the film-carrying mechanism in a separate soundproof compartment, the application of this method could be widely extended.

We have used the original machine on four patients with disease of the mitral valve, this disease was considered especially important because the mechanics of the valve lesion are not easily elucidated by the ordinary methods of study, and it seemed that such cases might give a fair idea of the value of graphic records of heart movement.

TECHNIC

The film-carrying apparatus was loaned to us by Dr Ruggles of the University of California, and operated with the assistance of Mr E P Fletcher. The method of operating this machine and of measuring the films and plotting graphically the motion perpendicular to the border of the heart of various points in the auricular and ventricular areas has been described elsewhere.⁴ Thirty feet of duplitized film are taken through the film carrier in two seconds, giving thirty exposures of one-fortieth of a second's duration each. However, due to the technical difficulties in running 30 feet of film through the present machine without mishap, ten rolls (300 feet) of film were used on these four cases. We have twenty-one consecutive exposures on case 1, twenty-four and twenty-six consecutive exposures on case 2, twelve and nineteen on case 3 and ten consecutive exposures on case 4. This gave us 3 heart cycles of case 1, a total of 5 cycles of case 2, a total of 28 cycles of case 3 and 13 cycles of case 4. The roentgenograms of cases 2 and 4 were satisfactory for accurate measurement. In case 1 the heart was so large that the right border is not on the films (8 by 10 inches [20 by 25 cm]). In case 3 the hilum and lung density interfered seriously with accurate measurement, so that the error was twice as great as in the normal or in the other three cases. The curves obtained from the two sets of film of this case were similar, and we felt that a good approximation of the motion of the heart had been reached.

REPORT OF CASES

CASE 1—Mr G H, aged 35, had had severe rheumatic fever in childhood, with mild recurrences almost annually during youth. He had been in a hospital for six months at the age of 24 for rheumatic fever, and for eight months at the age of 25 because of coughing and dyspnea. From the age of 26 to 31 he had worked hard (truck-driver), but had been in a hospital again for four months for cough and dyspnea. He returned to his previous work and continued at it until he entered the clinic, although for the last two years of that time he had had constantly recurring dyspnea and palpitation on exertion, and, at intervals of a few weeks, had had aching pain in the epigastrium for from two to three days at a time. This pain was worse two hours after meals and was relieved by rest. It became severe, and he entered the clinic eight months before our observations were made. The liver was tender and extended 4 cm below the right costal margin. There were no râles at the bases of the lungs. He was in a hospital for one month and returned to light work. Three months later he had acute bronchitis, with fever for ten days, and was in Lane Hospital for two weeks. He then returned to work, but had rather marked palpitation even on moderate exertion.

3 Lomon and Commandon. *La cinematographie radiologique*, J de radiol et d'electro 8 433 (Oct) 1924.

Physical Examination—The patient was a thin but muscular man. There was a definite malar flush and slight cyanosis of the lips. The apex beat in the left anterior axillary line was forceful, rapid and irregular, due to frequent extrasystoles, there was no thrill. The apical first sound was replaced by a harsh, loud systolic decrescendo murmur. The second sound was faint at the apex but loud at the pulmonic area. There was a soft low-pitched diastolic murmur, heard only outside the apex over a small area. It was loudest early and late in diastole, but audible throughout the entire diastole. The lungs were clear, the liver was not palpable. The diagnosis was rheumatic heart disease and mitral stenosis.

The electrocardiogram showed right ventricular preponderance. The vital capacity was 55 per cent. (Autopsy, eight months after roentgen cinematography showed that the mitral orifice consisted of a scarred and calcified opening of decidedly fixed size with a circumference of 7 cm. Regurgitation through such an orifice must have been marked.)

CASE 2—Mrs. T. G., aged 19, had not had rheumatic fever or chorea, but she had had severe "growing pains" for years during childhood. She lived on one of the highest hills in San Francisco and experienced slight dyspnea on walking up to her home. She had been married one year and had not been pregnant. For three months she had had severe palpitation on exertion or during excitement.

Physical Examination—The patient was small, fairly well nourished and of light frame. The coloring of the face was a little high. The tonsils were markedly enlarged, reddened and cryptic. (They were removed under local anesthesia, without any untoward sequelae, three weeks after our observations.)

The apex beat was in the fifth left interspace, just outside the midclavicular line. It was sharp, forceful, regular and 90 a minute. At the apex the first sound was loud and snapping, the second sound was fairly loud, and there was a high pitched, intense systolic murmur, sharply distinguished from the heart sounds but filling all of the systole. It was heard well in the axilla and was not transmitted to the midline, although audible along the left sternal border and in the pulmonic area. With the patient in a recumbent position, a soft, low presystolic murmur was heard in the fourth interspace, about 2 cm. inside the apex. The pulmonic second sound was sharply accented. The diagnosis was mitral stenosis.

The electrocardiogram was normal, the vital capacity was 72 per cent.

CASE 3—Mr. A. H., aged 28, had had rheumatic fever at the age of 5 years and again at the age of 12. There had been some dyspnea and palpitation on exertion since childhood. From the age of 16 to the age of 24 he did hard manual work (mill hand). For the next four years, he did only light work. For six months, he was increasingly short of breath and had several attacks of nocturnal dyspnea. He felt weak, and was unable to work, he then had acute bronchitis with fever for a week. He entered Lane Hospital at that time, remained one week after his fever subsided, and was then in a convalescent home for three weeks. He felt weaker than before his acute infection, and had had two attacks of nocturnal dyspnea during the week preceding our observation.

Physical Examination—The patient was a rather small, thin man, with definite cyanosis of the lips and fingertips. The apex beat was scarcely palpable, but there was a long purring diastolic thrill in the fourth and fifth left interspaces from 7 to 12 cm. from the midsternal line. The first sound at the apex was sharp and fairly loud. There was only a soft systolic murmur at the apex, not well heard over the rest of the precordium. There was a loud continuous rumble filling all of the diastole. The pulmonic second sound was slightly accentuated. There were fine râles at the bases of both lungs. The diagnosis was rheumatic heart disease, and mitral stenosis.

The electrocardiogram showed right ventricular preponderance, abnormally broad and high P waves. The vital capacity was 60 per cent.

CASE 4—Mr C, aged 28 (private patient of Dr A W Hewlett and Dr J K Lewis), had had rheumatic fever at the age of 19, valvular disease of the heart was demonstrated the following year. Dyspnea on exertion increased gradually. At the age of 25 it became marked, and he had had hemoptysis on three occasions. One year later, auricular fibrillation commenced, and regular rhythm was twice restored with quinidine. After fibrillation had occurred for the third time, Dr Hewlett discontinued the use of quinidine and prescribed digitalis. A right hemiplegia with aphasia came on during the night one month later. It gradually cleared up in about a week, but occasional slight dragging of the right foot remained. The patient was able to continue with his studies, though he tired easily and had occasional nocturnal dyspnea, as well as dyspnea on exertion.

Physical Examination—The patient was thin, with a slight frame and muscles. There was moderate cyanosis of the lips, ear lobes and fingers. The apex beat was in the anterior axillary line, absolutely irregular, about 95 a minute. There was a faint diastolic thrill and a continuous diastolic rumble, together with a soft systolic murmur, at the apex. The pulmonic second sound was loud, and there was a faint early diastolic murmur to the left of the sternum in the third interspace. The diagnosis was rheumatic heart disease, mitral stenosis, aortic insufficiency and auricular fibrillation.

The electrocardiogram showed auricular fibrillation and a normal ventricular complex.

CURVES ON ROENTGENOGRAMS OF THE HEART

The curves obtained by plotting the motion of points in the cardiac border against the time (one-fifteenth second for each exposure) are compared with the normal curves obtained from the roentgenograms of Dr Ruggles' subject. Noteworthy variation from the normal is not found in the ventricular areas. In the normal the upper part of the left ventricle continues to move mesad in early diastole, while the apex moves rapidly laterad. This is observed only in case 2, and there only for the first one-fifteenth of a second. We anticipated finding a change in the position of the "shoulder" on the diastolic rise in ventricular distention, but notable change is not found. Again we must emphasize the fact that the curve of motion of points on the ventricle does not in any way resemble the curve of volume changes in the ventricle as determined by the plethysmograph in animals, and that great variation is seen in motion of different points along the left ventricle, so that comparison of one case with another may be misleading. The total extent of motion of the left ventricle in cases 1 and 2 (chart 1) was roughly the same as in the normal, in case 3 (chart 2) and case 4 it was diminished. The right border moved in phase with the apex in cases 2, 3 and 4, though the total extent of motion in case 3 was slight (1.5 mm).

In case 4 we can find no point in the auricular area which moved out of phase with the ventricle. Dr J K Lewis points out to us that this is probably due to thrombosis in the left auricle. It will be recalled that this patient had had cerebral embolism two years previously.

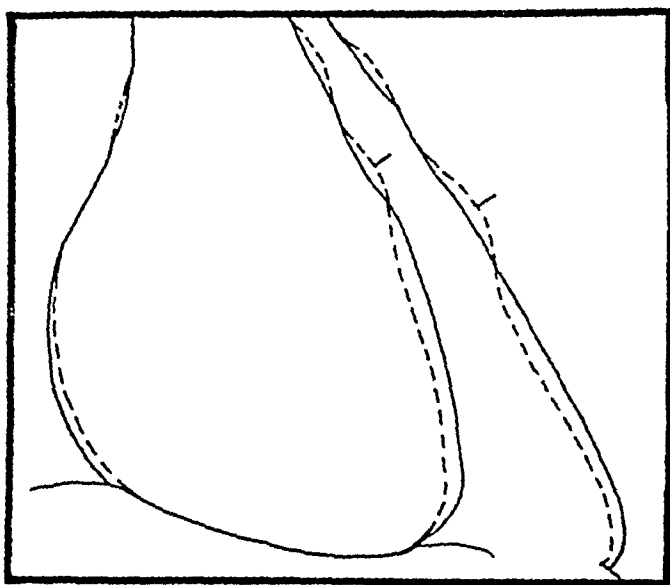


Chart 1—The curves on the right indicate the left border of the heart in case 1 on the left is shown the cardiac outline in case 2. The straight line denotes the end of diastole, the broken line the end of systole. Note the prominence of the left auricular and pulmonic artery areas at the end of systole in cases 1 and 2.

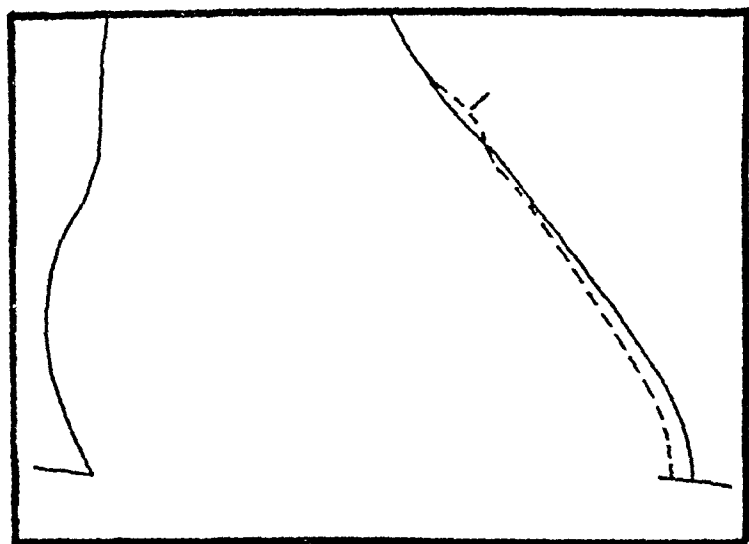


Chart 2—Cardiac outline of case 3. The straight line indicates the end of diastole, the broken line, the end of systole. Note the limited motion of the left auricular area.

Two consecutive cycles of case 2 and two cycles from different records of case 3 are shown in charts 3 and 4, to give an idea of the variation from cycle to cycle in a given case

In chart 5, graphic records of the motion of the left auricle, during systole and diastole in cases 1, 2 and 3 are compared with a correspond-

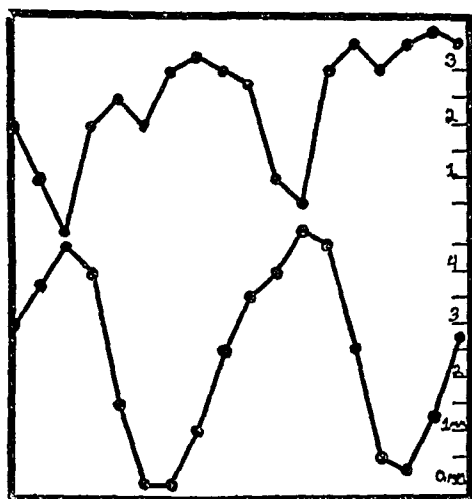


Chart 3—Two consecutive cycles of case 2, the upper curve showing motion of the left auricle, the lower curve, apical movement. Lateral movement is shown by upward swing of the curves. Each point represents one film or a duration of one-fifteenth second.

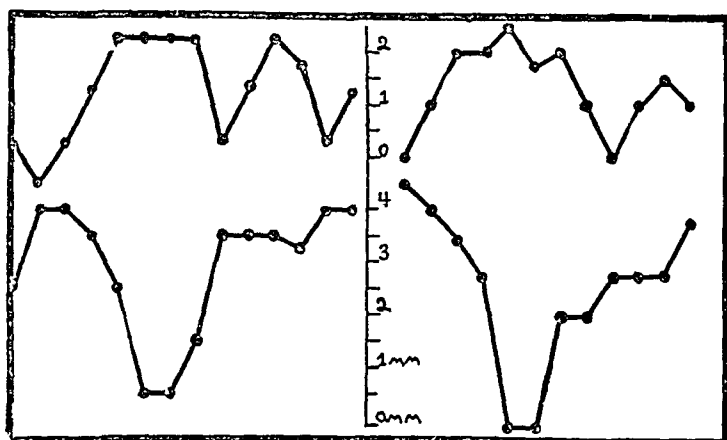


Chart 4 (case 3)—Two cycles, from two sets of films, showing, as in chart 3, auricular and apical movement.

ing record from the normal subject. It is immediately apparent from these curves that the auricular motion in cases of disease of the mitral valve is different from the normal. The motion of the auricle in case 3 is more like the normal than the other two, although clinically this patient presents the most typical case of stenosis of the mitral orifice. The early diastolic collapse, however, is less marked, and the mid-

diastolic distention and late diastolic (auricular systolic) emptying much more marked than in the normal

The most striking curves are those in cases 1 and 2, which, except for the difference in rate, are almost alike. In them the auricle does not empty rapidly in early diastole, but on the contrary continues to expand during the first one-fifteenth of a second. It then has an initially slow but increasingly rapid emptying, without any middiastolic "shoulder," and with only the increase in rate of late diastolic emptying to indicate the effect of auricular systole. With the onset of ventricular systole the auricle suddenly dilates, and then, after falling back slightly, continues a slower dilatation into early diastole.

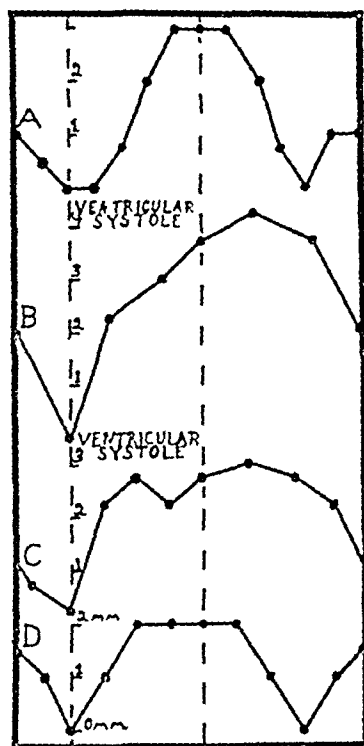


Chart 5—Schema comparing auricular motion of the normal heart (*A*), with the motion of the auricles of cases 1, 2 and 3 of disease of the mitral valve (*B*, *C* and *D*). The initial downstroke presumably represents the motion during auricular systole, and the time relationships of the curves of the abnormal hearts are distorted so as to give systole and diastole the same relative duration as the normal, one complete cycle being given. Each point represents one film or a duration of one-fifteenth of a second. *B* and *C* show the continuation of auricular filling into early diastole in the two cases of regurgitation, *D* the relatively prominent mid-diastolic filling and presystolic discharge in pure mitral stenosis in case 3.

COMMENT

Our observations, particularly with regard to motion in the left auricular area, indicate that important data can be obtained from careful measurement of the roentgenograms of the diseased heart obtained with Ruggles' roentgen cinematograph. The value of this method of study-

ing the effect of valvular lesions will be greatly increased when satisfactory films of oblique projections can be taken, and this applies particularly to mitral lesions. Comparison of the motion of the left auricle with the size and shape of the mitral opening may be expected to shed great light on the vexed problem of mitral regurgitation, but this will be possible only when cases can be studied during the last months of the patient's life. Whether the roentgen cinematograph is necessary for these studies or whether satisfactory curves can be obtained more easily by the slit and moving film method of Gott and Rosenthal⁴ has not been determined. The advantage of the cinematographic method is that it enables one to select any number of points in the cardiac outline for graphic analysis.

We can present no evidence with which to support our belief that the final emptying of the auricle is due to auricular systole, except that the time relationship of the final inward motion in the normal person and in case 3 corresponds approximately with that of auricular systole. Simultaneous electrocardiograms, on which the moment of each exposure is automatically recorded, should cast more light on this, as should also the form of the auricular curve of heart border motion in cases of auricular fibrillation without valvular lesion.

In case 3 the form of the auricular motion curve points definitely to mitral stenosis. The diminished rate and extent of early diastolic emptying and the great accentuation of that part of the curve supposedly due to auricular systole are to be expected with advanced anatomic stenosis, practically without regurgitation. Classic physical and electrocardiographic changes were found in this patient, but the teleroentgenogram was hardly more than suggestive of a mitral lesion, and there was no such bulging of the left auricular area as in cases 1 and 2. Of the latter cases, the first had a murmur audible throughout diastole, the second only in late diastole, in both the murmur was sharply localized near the apex and unaccompanied by a thrill. These observations are usually considered sufficient for the diagnosis of mitral stenosis, but this is not borne out by the roentgenograms of the heart. In both instances auricular movement is rapid and marked, and the rapid dilatation in early systole points definitely to regurgitation. This is further borne out by the sequence of events in diastole, the absence of any evidence of auricular systole except the increase in rate of mesad motion in late diastole, and the fact that dilatation continues for one-fifteenth of a second into early diastole. The latter finding was a puzzle to us at first,

4 Gott, T. H., and Rosenthal, J. Ueber ein Verfahren zur Darstellung der Herzbewegung mittels Rontgenstrahlen (Rontgenkymographie). *München med. Wchnschr.* 59: 2033, 1912.

but agrees exactly with Wiggers and Feil's⁵ demonstration in animal experiment that mitral regurgitation continues from 0.08 to 0.09 seconds after the end of systole. The only evidence of mitral stenosis in the auricular movement of cases 1 and 2 was the relatively slow collapse when diastolic emptying had commenced. This is at once apparent on comparing these curves with the normal or with curves of auricular volume in experimental mitral insufficiency.⁵

In the analysis of the normal curve we had suggested² that one reason that the upper part of the ventricle moved mesad while the apex moved laterad in early diastole might be that the blood, streaming in along the long axis of the heart, might push out the apex and hence cause a narrowing of the upper part of the ventricle. In case 2 a similar phenomenon seems to be due, in part at least, to diastolic relaxation of the ventricle, the apex falling away from the base and the lateral wall inward as the contraction dies out, but this occurs while the auricle is still dilating.

We recognize that from one normal and three abnormal cases only tentative conclusions can be drawn. Further work will undoubtedly show wide variations in normal as well as in diseased hearts, yet there seems to be no doubt that a study of the curves of heart border motion offers a relatively accurate means of distinguishing mitral regurgitation from mitral stenosis, these terms being taken in the physiologic sense. Such a distinction has lapsed in some clinics, largely as a reaction to the former practice of making too frequent and often erroneous diagnoses of mitral regurgitation merely on the basis of a systolic murmur. Those who have led this reaction point out that practically all organic mitral lesions result in a narrowing of the orifice, and that regurgitation in the presence of organic stenosis of whatever degree had better be ignored. Elsewhere and particularly in Europe, the diagnosis of mitral regurgitation is seriously considered in patients with myocardial failure and a prominent auricular area in the left border of the heart, whether determined by the roentgen ray or by percussion, and in patients with rheumatic valvular disease with loud systolic murmurs. Sprague and White⁶ have recently discussed the entire question. It is their belief that mitral insufficiency can be diagnosed from the history and physical observations, and is a less serious lesion than stenosis. Our observations tend to give weight to Balfour's view⁷ that mitral regurgitation has a definite character, and that "the only unequivocal proof of the existence of

5 Wiggers, C. J., and Feil, H. The Cardiodynamics of Mitral Insufficiency, *Heart* 9 149, 1921.

6 Sprague, H. B., and White, P. D. A Comparative Study of "Rheumatic" Mitral Regurgitation and Mitral Stenosis, *Am. Heart J.* 1 629 (June) 1926.

7 Balfour, G. W. Clinical Lectures on Diseases of the Heart and Aorta, London, 1876, p. 154.

actual disease of the mitral valves is the determination of the existence of an auricular-systolic, or as it is commonly termed, a presystolic murmur" He held, and we believe that it is a safe guide for the present time, that this is as true of mitral regurgitation (due to disease of the valve itself) as of mitral stenosis

Clinical and experimental evidence is being advanced to prove the seriousness of mitral regurgitation Gussenbauer⁸ described a case of mitral insufficiency due to a gunshot in which an oval hole in the anterior mitral leaflet, not more than two-thirds the area of the aortic orifice, led to heart failure, auricular fibrillation and death in ten years This patient did not have a syphilitic or rheumatic myocarditis, and there was an extraordinary dilatation of the left auricle This shows the seriousness of such a lesion⁹ Of 147 patients with mitral stenosis whose hearts were examined at autopsy and reported on by Cabot,⁹ eighty had mitral orifices of greater circumference than the traumatic aperture in Gussenbauer's case It is noteworthy that our patient with pure mitral stenosis did not have any significant prominence of the auricular region, while the two patients in whom regurgitation was preponderant had the classic "mitral configuration" Experimentally, Allan¹¹ has shown recently how easily mitral stenosis is compensated until the aperture is reduced to minute size, and what a comparatively large load is put on the heart by regurgitation

The importance of developing accurate clinical criteria for the differential diagnosis of mitral stenosis and mitral regurgitation is apparent This is of utmost importance to those who attempt operation on the heart, for it will enable them to spare from operation patients whose lesions mainly produce regurgitation The difficulty has been discussed by Souttar¹² whose patient had a mitral orifice which easily admitted a finger

SUMMARY

A study of the curves of heart border motion constructed from films taken with Ruggles' roentgen cinematograph shows that in mitral disease the motion of the auricular region is of great significance

8 Gussenbauer, R Ein Fall von traumatischer Mitral insuffizienz, *Wien med Wchnschr* **75** 134 (Jan 10) 1925

9 Adam A Ueber die traumatischen Veränderungen gesunder Klappen des Herzens, *Ztschr f Kreislaufforsch* **9** 313 (May) 1927

10 Cabot, R Facts on the Heart, Philadelphia, W B Saunders Company, 1926, p 76

11 Allan, G A A Schema of the Circulation with Experiments to Determine the Additional Load on the Apparatus Produced by Conditions Representing Valvular Lesions, *Heart* **12** 181, 1926

12 Souttar, H S Surgical Treatment of Mitral Stenosis, *Brit M J* **2** 603 (Oct 3) 1925

A patient with a marked thrill and loud diastolic murmur, but slight systolic murmur, gave curves which are interpreted as those of mitral stenosis

Two patients with loud systolic and soft localized diastolic murmurs gave curves which apparently indicate the preponderance of regurgitation. In one of these autopsy (eight months after our studies) revealed a mitral orifice with a circumference of 7 cm held open by a scarred and calcified margin

MATERIAL FROM LYMPH NODES OF MAN

I METHOD TO OBTAIN MATERIAL BY PUNCTURE OF LYMPH NODES FOR STUDY WITH SUPRAVITAL AND FIXED STAINS*

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This paper deals with a method for obtaining living tissue from lymph nodes and tumors, and emphasizes the importance of studying living cells in pathologic processes. The results obtained from the study of abnormal lymph nodes by the application of these methods are discussed in a separate communication¹

Lymph nodes of patients usually are studied for diagnosis by ordinary pathologic technic after their surgical removal. Biopsy is not a procedure that can be repeated readily, and thus in following the development of disease processes, or the effect of therapy, it is not a satisfactory way of obtaining tissue for pathologic study. Furthermore, biopsy is refused by many patients, and is frequently difficult and at times impossible to perform with safety. Moreover, the usual technic for accurate diagnosis from the tissue obtained by biopsy requires several days. For these reasons material has been obtained from lymph nodes by puncture. This procedure has none of the disadvantages of biopsy, is simple, and seldom is objected to by patients, probably because they have no apprehension concerning the use of a needle such as they have concerning a procedure involving the use of the surgeon's knife. Puncture can be performed repeatedly and safely in many cases in which surgical removal of the node would be unwise or difficult. The cellular material obtained can be studied both in fixed and in fresh preparations. The living cells supravitaly stained have furnished new and useful information. By such procedures much may be learned and a diagnosis probably made in less than half an hour, in contrast to several days required by the technic for the usual pathologic diagnosis. Whether the knowledge obtained by studying cellular material from nodes will be as serviceable as that deduced from examining sections of a lymph node, can be decided only after many comparisons and observations have been made.

* From the Medical Service of Collis P Huntington Memorial Hospital of Harvard University

1 Forkner, C E. Studies on Living and Fixed Cells Withdrawn from Lymph nodes of Man, to be published

HISTORY OF PUNCTURE OF LYMPH NODES

Puncture of lymph nodes seems to have been confined especially to schools of tropical medicine. Aspiration of material from nodes apparently was first undertaken by Grieg and Gray in 1904,² in order to isolate the etiologic agent of trypanosomiasis. Since then, numerous investigators have aspirated lymph nodes with a syringe and needle to recover the organisms of certain tropical diseases and of syphilis. None of those physicians, however, has reported on the cellular material obtained. Ward, in 1912,³ suggested that the appearance of cells obtained by puncture of nodes might aid in the diagnosis of the various forms of lymphoblastoma. He was aware of one such case in which the procedure was performed without ill effect. Guthrie, in 1921,⁴ made a serious attempt to study the tissue cells obtained by aspiration from patients' lymph nodes. He has described the appearance in fixed stained preparations of the cells he withdrew in different forms of lymphoblastoma and conditions simulating them. From the material obtained he was able to make the diagnosis of Hodgkin's disease—a type of lymphoblastoma according to some authorities. Guthrie's important report is of a preliminary nature, however, and leaves many matters inconclusive.

Guthrie⁴ punctured lymph nodes with a 21 gage needle on the end of a syringe, rotated it once, and then by negative pressure withdrew into the syringe as much material as possible. He says that in many cases a scant amount of material was obtained because of the firm consistency of the tissue. This difficulty was only too apparent when I began puncturing nodes by this method, and sometimes tissue could not be obtained, or the amount was insufficient for adequate study. I have almost invariably been able to obtain enough material by employing a barbed dental broach passed through the lumen of a small needle inserted into the substance of the node. Large numbers of living cells are withdrawn easily on the barbs. Other methods of puncture were tried, but the following was adopted as the most satisfactory.

TECHNIC

The procedure which has been developed and utilized in studies on lymph nodes is as follows. The skin overlying the structure to be punctured is cleaned surgically by scrubbing with soap, followed by the application of ether and iodine, or by mercuric chloride or picric acid solutions. About 0.5 cc of procaine hydrochloride in solution is infiltrated through a small hypodermic needle into the skin. A 17 or 18 gage sterile needle about 3.5 cm in length is then inserted

2 Grieg, E. D. W., and Gray, A. C. H. *Brit. M. J.* **1**: 1252, 1904. Lymphatic Glands in Sleeping Sickness, *Lancet* **1**: 1570, 1904.

3 Ward, G. R. *Bedside Haematology*, Philadelphia, W. B. Saunders Company, 1914, p. 129.

4 Guthrie, C. G. Gland Puncture as a Diagnostic Measure, *Bull. Johns Hopkins Hosp.* **32**: 266, 1921.

through the anesthetized area until the point pierces the capsule of the lymph node or diseased tissue. The exact position of the needle point is easily determined by the resistance it encounters and by the movability of the mass. After the needle has been passed just within the tissue from which material is desired, the needle is steadied and a sterile coarse dental broach⁵ is passed through the lumen. These broaches are constructed so that they enter the tissue like a needle, but come out like a fish hook, carrying on the barbs numerous elements of living tissue. Smears of the material obtained are then quickly made on glass coverslips. One puncture of a tumor or node yields sufficient material for several smears. The more cellular the tissue the more material is obtained from which cultures as well as smears may be made. After sufficient material has been obtained by inserting one or more broaches, the needle is withdrawn and a small dry sterile dressing applied. The procedure seems to be no more painful than puncturing a vein in the arm for the withdrawal of blood, and there has been no difficulty in making repeated punctures of lymph nodes on the same patients.

VALUE OF STUDIES ON LIVING CELLS

The particular studies made on the material collected by this type of puncture have been observations of fixed smears stained with Wright's stain and supravital stained preparations. Heretofore, information has not been reported concerning living cells from human lymph nodes examined by the aid of supravital stains. Webster⁶ and Lewis and Webster⁷ made studies on the lymphocytes in tissue cultures of normal and pathologic lymph nodes. They observed that lymphocytes were capable of migrating into the plasma clot from "explanted pieces of lymph-nodes." Webster⁶ believed that evidence of ameboid activity on the part of the lymphocytes was indicative of a rapidly fatal course. These authors have not reported any studies concerning the reaction of living cells of lymph nodes to vital dyes. It would appear to be possible to acquire physiologic as well as histologic knowledge of a new sort by this means. For example, observations may be made on ameboid activity, phagocytic power, behavior to altered environment, resistance or susceptibility to staining and other characteristics. It is not possible adequately to obtain such information from observations on fixed tissues. Thus a definite opinion can be arrived at concerning the age, stage of development and activity of the cells.

The ordinary histologic methods require that tissues be subjected to rigorous measures, which not only obscure the physiologic processes of

⁵ The dental broaches are obtainable from almost any dental supply company. Broaches with aluminum handles are the most satisfactory. For these studies the "Dayton Dental Broach-Improved-Coarse-Style Number 1" has been used.

⁶ Webster, L. T. Lympho-sarcoma, Lymphatic Leukemia, Leukosarcoma, Hodgkin's Disease, *Bull. Johns Hopkins Hosp.* **31** 458, 1920.

⁷ Lewis, W. H., and Webster, L. T. Migration of Lymphocytes in Plasma Cultures of Human Lymph nodes, *J. Exper. Med.* **33** 261, 1921.

cells but also produce artefacts. If one contrasts the study of living cells with that of dead cells, the protoplasm of which has been coagulated by strong fixing agents, altered by dehydration and shrinking in alcohol and subjected to abnormal processes in embedding and then cut at various angles, the value of studying living cells becomes apparent. Like any procedure, practice and experience is required to make accurate and reliable observations on living supravitaly stained cells.

The behavior of blood cells to vital dyes was studied as long ago as 1902 by Rosin and Bibergeil,⁸ but it is the work of Evans and Scott,⁹ Simpson¹⁰ and Sabin¹¹ which has developed efficiently the so-called supravital method. These workers and their pupils have shown the value of the method and contributed much information concerning living blood cells. Details of technic are given by Simpson¹⁰ and Sabin¹¹. I shall give a brief description to indicate its nature and the modifications found useful for studying lymph node material.

A thin film of dye in alcoholic solution is smeared across the surface of a previously cleaned, polished and warmed glass slide. This is done by dipping the end of another slide, with which the smear is made on the former one, into a fresh mixture (10 drops) of equal parts of 0.5 per cent alcoholic solution of neutral red and a 0.1 per cent alcoholic solution of Janus green. Solutions of the dyes are kept on hand, made up in 95 per cent alcohol. The dyes are not mixed until they are ready for use, because a mixture is not a stable preparation. Solutions of varying concentrations should be employed for making the dye films until one has gained proficiency in estimating the optimum concentration desired. Emphasis should be placed on staining the cells as lightly as is consistent to obtain good differentiation of the structures they contain. If the dyes are employed in concentrated solutions, the nuclei will be stained and the cells quickly killed. The glassware must be scrupulously clean because cells are delicate structures, and any acid, alkali or the like will injure their membranes and markedly alter their physiologic behavior.

METHOD MODIFIED FOR TISSUE CELLS

In the study of cells from blood, a free-flowing drop of blood is procured on the under surface of a glass coverslip, and this is allowed to fall gently on the slide prepared with the dye. In the case of blood, the plasma takes up some of the dye and acts as a medium in which the cells maintain their activity in suspension. However, material obtained from nodes, especially if fibrosed, often has

8 Rosin, H., and Bibergeil, E. *Ergebnisse vitaler Blutfärbung*, Deutsche med. Wchnschr. **27** 41, 1902. Rosin, H. *Das Verhalten der Leucocyten bei den vitalen Blutfärbungen*, Virchows Arch. f. path. Anat. **178** 478, 1904.

9 Evans, H. M., and Scott, K. T. *On the Segregation of Macrophage and Fibroblast Cells by Means of Vital Acid Dyes and on the Cause of the Differential Effect of These Substances*, Anat. Record **16** 148, 1919.

10 Simpson, M. E. *Vital Staining of Human Blood with Special Reference to the Separation of the Monocytes*, Univ. Calif. Pub. Anat. **1** 1, 1921.

11 Sabin, F. R. *Studies on Living Human Blood Cells*, Bull. Johns Hopkins Hosp. **34** 277, 1923.

insufficient fluid to permit cells to be properly suspended. The addition of physiologic sodium chloride alters the staining qualities and behavior of the cells, and is not ideal for this purpose. As a fluid in which to suspend the cells one can use the patient's serum or that from a person belonging to iso-agglutination group I (Moss classification) whose serum does not agglutinate red blood corpuscles. I have also used successfully sterile clear fluid obtained from ovarian cysts. It is essential to have a fluid medium in which to suspend the cells immediately after their removal from the body in order to prevent desiccation and to promote a uniform staining reaction.

The staining properties of blood cells and their physiologic response to dyes are excellently described by Simpson¹⁰ and Sabin,¹¹ and for such information reference should be made to their articles. Suffice it to say here that Janus green and neutral red are relatively nontoxic dyes, the former in dilute concentrations is a specific stain for mitochondria, and the latter a specific one for cytoplasmic structures. Their application to tissue cells is discussed in the subsequent article.

INDICATIONS AND CONTRAINDICATIONS FOR PUNCTURE

The safety of puncturing lymph nodes of various sorts has been considered carefully, and it appears that this procedure is to be looked on as harmless if used with discretion. One must be acquainted with the anatomy of the given region before attempting to make a puncture. About forty punctures have been made in nodes proved by sections to be diseased with various types of lymphoblastoma, metastatic cancer and other tumors, myelogenous leukemia, tuberculosis and simple hyperplasia. Local or general dissemination of a tumor or spread of disease which could be attributed to puncture has not been observed. There is no evidence that infection, hemorrhage into nodes or significant discomfort has occurred. Biopsy in some cases of lymphoblastoma and metastatic cancer may be followed by a rapid spread of the disease, and perhaps eventually this may be shown to result from puncture. Puncture, however, requires less manipulation and trauma than surgical removal of a lymph node.

Puncture of lymph nodes seems contraindicated in cases of probable or definite malignant disease when the possibility of cure by total removal of the pathologic tissue exists. It is best not to injure such neoplasms. Another contraindication is immediate proximity of the structure to be punctured to a large artery. The exact location of the needle point can usually be accurately ascertained, and thus one need not be alarmed if an artery is nearby.

Puncture of a node does not interfere with its subsequent removal. This sequence of events has taken place in several of the cases studied in order to correlate the results obtained from material collected by puncture with those recorded from observations of sections of nodes.

prepared by the usual pathologic technic. Such correlations in many more cases than I have studied are essential before a final opinion concerning the value of puncture of lymph nodes can be decided. The procedures referred to, however, appear to be of some service as indicated in my second paper.

SUMMARY

Puncture of lymph nodes by means of a hollow needle through which a dental broach is passed is a new, apparently harmless and satisfactory way to obtain sufficient material from patients for study.

The value of studying the living cells from diseased lymph nodes by supravital staining is emphasized.

DIABETES MELLITUS

INCIDENCE AND CERTAIN ETIOLOGIC FACTORS

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AND

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Great interest has been manifested in various problems bearing on the etiology of diabetes mellitus, especially during the last few years. This is due largely to the menace of the disease as revealed by the increase in its incidence as well as in its mortality rate, at least until the time of the introduction of insulin ¹

The observations of Emerson and Larimore ² have definitely proved that there has been a progressive and actual increase in the death rate from diabetes in New York, as well as in other larger cities, between the years 1860 and 1923. They direct attention to the fact that an increase in the death rate from a certain disease may be considered as pointing to an actual increase in its incidence, especially during a period in which clinical diagnosis as well as treatment have progressed to such an extent as to make possible early recognition of the disease, arrest in early cases and postponement of death when cure cannot be expected. This, they point out, can be assumed to be true of diabetes, since great advances have been made in both diagnosis and treatment.

Table 1 presents the average death rate from diabetes per 100,000 population for Baltimore, Philadelphia and New York for twenty years in five year periods. It is evident that there was a progressive increase in the mortality rate of the disease until 1923, it was greater in Baltimore than in Philadelphia, and greater in Baltimore than in New York since 1910.

Table 2, furnished through the courtesy of Dr C Hampson Jones, commissioner of health of Baltimore, demonstrates that notwithstanding

¹Presented at the Meeting of the American Gastro-Enterological Association at Atlantic City, May 3, 1927

²From the Gastro-Enterological Clinic of the Department of Medicine of the University of Maryland, Baltimore

1 The Metropolitan Life Insurance Company ascribes the lowering in the death rate from diabetes among their industrial policy holders during the last half of 1923 and the first quarter of 1924, to the successful and widespread use of insulin (Statistical Bulletin Metropolitan Life Insurance Company, vol 5, no 2, [Feb] 1924)

2 Emerson and Larimore Diabetes Mellitus, Arch Int Med **34** 585 (Nov) 1924

a fall from 21.01 to 14.41 in the general death rate in Baltimore from 1900 to 1924 (i. e., deaths from all causes for each 1,000 of the population), there was a rise from 6.9 to 24.2 in the death rate from diabetes for each 100,000 of population. The death rate per 100,000 from this dis-

TABLE 1—Average Death Rate from Diabetes per 100,000 Population for Baltimore, Philadelphia and New York for Twenty Years, According to Five Year Periods*

	1900 to 1904	1905 to 1909	1910 to 1914	1915 to 1919	1920 to 1924
Baltimore	9.3	12.4	16.8	20.3	23.8
Philadelphia	9.1	11.2	15.5	15.0	17.0
New York	12.3	11.8	17.0	19.8	21.4

* The Philadelphia and New York figures are taken from Anders and Jameson.²

TABLE 2—Deaths and Death Rates from all Causes and from Diabetes in Baltimore, from 1900 to 1924

Year	Popula- tion	Total Deaths All Causes	Crude Death Rate per 1,000	Deaths from Diabetes			Diabetes Death Rate per 100,000	Percentage Dia- betes Deaths of All Deaths	Age Groups					
				Total	Male	Female			0 to 19 M F	20 to 44 M F	45 M	45 F	45 M	45 F
1900	509,375	10,700	21.01	35			6.9	0.33						
1901	514,390	10,479	20.37	49			9.5	0.47						
1902	519,406	10,253	19.74	46			8.9	0.15						
1903	524,421	10,141	19.31	55			10.5	0.51						
1904	529,437	10,818	20.43	57			10.8	0.53						
1905	534,452	10,695	20.01	56			10.5	0.52						
1906	539,468	10,753	19.93	72			13.3	0.67						
1907	544,483	11,190	20.55	83			15.2	0.71						
1908	549,499	10,435	18.99	61			11.1	0.58						
1909	554,514	10,376	18.71	67			12.1	0.65						
1910	559,530	10,753	19.22	93			16.6	0.86						
1911	564,545	10,401	18.43	98			17.1	0.91						
1912	569,560	10,441	18.33	88			15.5	0.81						
1913	574,576	10,679	18.59	87			15.1	0.82						
1914	579,592	10,551	18.20	115			19.8	1.09						
1915	584,607	10,002	17.11	109	45	64	18.6	1.09	3	1	8	7	31	55
1916	589,623	10,719	18.18	122	51	68	20.7	1.11	2	1	10	7	12	57
1917	594,638	11,361	19.11	124	56	68	20.9	1.09	3	2	10	7	13	59
1918	599,653	16,032	26.71	119	48	71	19.8	0.71	2	3	9	10	37	58
1919	609,961	11,434	17.07	115	54	91	21.6	1.27	3	1	7	16	11	74
1920	740,172	11,356	15.34	155	61	91	20.9	1.36	2	2	11	11	51	78
1921	752,865	10,389	13.78	169	58	111	22.1	1.63	1	1	7	12	50	95
1922	762,222	10,821	14.20	200	71	129	26.2	1.85	5	5	5	8	61	116
1923	773,589	11,588	14.98	195	82	113	25.2	1.68	3	2	9	9	70	102
1924	784,938	11,310	14.41	190	59	131	24.2	1.68	1	3	11	8	47	120

ease was, therefore, more than three times greater in 1924 than in 1900. It will also be noted that the number of deaths from diabetes in 1924 (190) exceeded those of 1900 (35) more than five times, while the population of the former year was but little over one and a half times larger than that of the latter year. A more marked increase was noted

by Anders and Jameson³ in their mortality figures for Philadelphia. As Emerson and Larimore have pointed out, while this increase in the incidence of the death rate has included persons of all ages, it has been marked in women at all ages and in men over 45. Our observations have confirmed these facts.

According to the statistics furnished by the Bureau of Census⁴ of Washington, the death rates from diabetes show a steady increase upward between 1910 and 1920. Most of this increase is due to the higher rates above the age of 45, the menace of the disease being more especially noted among women over that age.

Joslin⁵ attributes this increase in diabetes to a number of factors: (1) to a greater accuracy of vital statistics, (2) to urinary examinations more frequently performed as a routine, (3) to the general increase, in longevity, which should necessarily add to the incidence of this disease, (4) to life insurance examinations and statistics through which the recognition of new cases has more frequently been made possible, and (5) to the frequency by decades at which the onset of this disease occurs at the present time, which has likewise made comparatively greater the increase of cases in the first decade as compared with the increase shown in former statistics. Among the interesting problems associated with the etiology of diabetes is the well recognized observation of the greater hazard of this disease among the Jewish as compared with the non-Jewish population. The disease has been significantly termed "Juden-Krankheit", because of the great prevalence of this condition among the Jews.

As the tabulations in New York and in other cities do not include the religious belief of the deceased (not noted in the death certificates), it is impossible, according to Emerson and Larimore, to obtain a wholly reliable basis for the calculation of the death rates by races. On the other hand, these observers point to an interesting correlation in New York City and Boston between the increase in the percentage of Jews in the population over a period of years and the increase in the death rates from diabetes for the same years in the two cities.

According to Emerson and Larimore, it would seem, "to be more than an unrelated coincidence that a city like New York with more than half of all of the Jews of the country, has shown in the last thirty years a greater increase in diabetes death rates than any other large city, and a percentage increase of rate running parallel with the percentage of difference in the Jewish element in the population."

³ Anders and Jameson. *Am J M Sc* **170** 313 (Sept.) 1925.

⁴ Department of Commerce, Bureau of Census Mortality Rates, 1910-1920, 1923, p. 87.

⁵ Joslin. *Treatment of Diabetes Mellitus*, Philadelphia: Lea & Febiger, 1923, p. 121.

The testimony of many observers tends to corroborate the fact that diabetes occurs more frequently among the Jews. According to Morrison,⁶ there were 1,775 deaths from diabetes in Boston from 1895 to 1913. Of these, 127 occurred among the Jews, among whom the total number of deaths was 6,936 while 1,648 occurred among the Christians, among whom the total number of deaths was 222,532.

The ratio of the number of deaths from diabetes to the total number of deaths from all causes is 0.018 among Jews and 0.007 persons who are not among Jews, diabetes has, therefore, been two and one half times as frequent a cause of death among the Jews as among the rest of the population.

The reports abroad of Auerbach,⁷ Wallach,⁸ Singer,⁹ Frerichs,¹⁰ Kulz,¹¹ and Van Noorden¹² indicate the greater incidence of diabetes in the Jewish race as compared to other races. In this country, Stern,¹³ Rudish and Aronson,¹⁴ Billings,¹⁵ and Joslin¹⁶ have arrived at a similar conclusion.

The cause of the special susceptibility of the Jews to this disease has not yet been satisfactorily determined.

According to Emerson and Larimore, "sedentary occupations, unsuitable dietary habits, luxurious living, disinclination to indulge in physical exercise, a marked tendency to obesity in men and women among the Jews, particularly after 45 years of age, may well be more definite etiologic factors in the apparent excess of diabetes death-rates among the Semitic people than their race."

S. Solis Cohen¹⁷ attributes the disproportionate prevalence of diabetes, first, to unsuitable dietetic habits brought over by the Jewish immigrants from Russia, which to a great degree accounts for the coincident obesity, and secondly, to the emotional disturbances due to centuries of persecution which produced an autonomic endocrine imbalance.

6 Morrison. Boston M & S J **175** 55 (July 13) 1916

7 Auerbach. Ztschr. Demogr. Stat. Juden, 1908, p. 164, quoted by Fishberg. The Jews, A Study of Race and Environment, 1911, p. 298.

8 Wallach. Deutsche med. Wchnschr. **19** 779, 1893.

9 Singer. Krankheitslehre der Juden, Leipzig, 1904, p. 81.

10 Frerichs. Ueber den Diabetes, Berlin, 1884, p. 185.

11 Kulz. Klinische Erfahrungen ueber Diabetes Mellitus, Jena, 1899, p. 2.

12 Van Noorden. Zuckerkrankheit und Ihre Behandlung, Ed. 6, Berlin, 1912, p. 54.

13 Stern. M. Rec. **58** 766 (Nov. 17) 1900.

14 Rudish and Aronson. Mt. Sinai Hosp. Rep. **11** 26, 1899-1900.

15 Billings. United States Census Bulletin, Vital Statistics of the Jews in the United States **19** 15 (Dec. 30) 1890.

16 Joslin. Diabetic Problem of Today, J. A. M. A. **83** 727 (Sept. 6) 1924.

17 Cohen, S. Solis, in discussion on Anders and Jameson. J. A. M. A. **84** 1776 (June 6) 1925.

Von Noorden¹⁸ believes that the frequent racial intermixture of Jewish with other blood is the cause of the excessive prevalence of diabetes among the Jews, while others attribute it to the frequency of consanguineous marriages. In analyzing the predominant factors associated with the etiology of diabetes, Joslin¹⁹ calls attention to the fact that many of these, especially observed in the Jewish race, such as the occurrence of this disease in the conjugal form, its presence among the wealthier classes, its hereditary tendency, its occurrence in mental workers in contradistinction to physical workers and as a sequel to infectious diseases, can all be readily accounted for on the basis of an associated obesity.

The relationship between diabetes and obesity has been exhaustively studied by Joslin¹⁹. A study of the weight of his adult diabetic Jewish patients before the disease manifested itself indicates that they were more obese than the patients who were not Jewish. Joslin says that "85 per cent of the Jewish patients were overweight in contrast to 70 per cent of a mixed series of 1,000 Gentiles, 47 per cent of these were underweight in contrast to 12.2 per cent of the non-Jewish patients." According to Joslin, if diabetes were especially characteristic of the Jewish race, it would be noted equally from youth to old age, however, in comparing the age incidence of this disease in 2,611 of his patients of all nationalities, he noted that instead of a parallel incidence through all the life periods, it was less common among the Jews in the first two decades of life, but more frequent during the fourth and fifth decades. The Jewish child is, therefore, no more likely to become a victim of this disease than the child who is not Jewish. On the other hand, the Jewish patient contracts the disease, not because of his race, but because of obesity.

Joslin also calls attention to the significant fact that the death rates from diabetes are essentially the same in New York and in Boston, notwithstanding the fact that three tenths of the population of New York is Jewish and but one tenth of that of Boston. On the other hand, in Brookline, in which the Jewish population is scarcely proportionately larger than in Boston, the death rate is double, undoubtedly due to the proportionately greater number of older, wealthier and more obese Jews.

In this connection the studies of Anders and Jameson²⁰ are of especial interest, they made the observation that the average percentage of overweight is higher among the Jewish women with diabetes than among the men, and that the incidence of diabetes among the obese Jews is higher than among the obese Gentiles, the ratio being 12 to 8.

18 Von Noorden. *Berl klin Wchnschr* **37** 1117, 1900.

19 Joslin. *Prevention of Diabetes*, J A M A **76** 79 (Jan 8) 1921.

20 Anders and Jameson. (Footnote 3, p 319).

The relation of obesity to diabetes becomes still further evident in the study of sugar tolerance curves in obese persons. According to John,²¹ the maximum increase in the blood sugar concentration in the nondiabetic person occurs promptly following the ingestion of 100 Gm of dextrose—in 58 per cent of cases in one-half hour, in 33 per cent, in one hour, and in 8 per cent, in two hours. In diabetic persons the rise in blood sugar concentration is slow, as is also the return to the normal level. In only 3.8 per cent of cases did the maximum rise appear one-half hour after the ingestion of the dextrose, in 15.4 per cent, it appeared at the end of one hour, in 54 per cent, at the end of two hours, and in 23 per cent, at the end of three hours. According to this observer, if the curve returns to the normal level in three hours following the ingestion of 100 Gm of dextrose, the person is considered not diabetic, if more than three hours is required, he is considered diabetic. The cases in which the return to the normal level occurs in about three hours are recorded as being in the prediabetic stage.

Paullin and Sauls,²² in a study of the blood sugar tolerance to dextrose, arrive at a somewhat similar conclusion in the study of twenty-six obese persons, of whom 57.6 per cent gave an abnormal response to the ingestion of dextrose. Six of the persons were classified by this method as having early cases of diabetes.

Beeler and Fitz²³ also observe that a certain group of obese persons present a curve of glycemia following the ingestion of 100 Gm of dextrose resembling that of mild diabetes.

It is evident from these observations that a prediabetic stage may be recognized in a certain number of obese persons.

Following the observations of Paullin and Sauls, we have made a study of blood sugar tolerance to dextrose, noting especially the curve of glycemia, in forty-five obese Jews whose weight was compared with the standard weight of a person of the same age and height as noted in the table of the Association of Life Insurance Directors and Actuaries of America. The result of our observations are noted in table 3. Of the twenty-five persons, thirty-one, or 68 per cent, gave an abnormal response to the ingestion of the dextrose, of these, eight were found to have early diabetes. The abnormal response is indicated by an increase in sugar of over 0.17 per cent following the ingestion of dextrose, the curve for sugar is high and rather sustained, and a longer period is required for its return to normal, glycosuria is usually present.

21 John. J. *Metab. Research*, **4**: 286 (Sept.-Oct.) 1923, *Am. J. M. Sc.* **173**: 184 (Feb.) 1927.

22 Paullin and Sauls. *South. Med. J.* **15**: 249 (April) 1922.

23 Beeler and Fitz. *Glycemia, Glycuresis and Water Excretion in Obesity*, *Arch. Int. Med.* **28**: 804 (Dec.) 1921.

TABLE 3—*Blood Sugar Tolerance Tests in Forty-five Obese Jews of from 12 to 67 Per Cent Overweight, Arranged According to the Percentage of Overweight*

No	Name	Sex	Age	Weight	Pounds Over Weight	Per Cent Overweight	Blood Sugar After 100 Gms Dextrose					Urinary Examinations After 100 Gms Dextrose				
							Fasting	1/2 Hour	1 Hour	2 Hours	3 Hours	Fasting	1/2 Hour	1 Hour	2 Hours	3 Hours
1	S M	♂	63	164	18	12	0.110	0.142	0.145	0.120	0.100	0	0	0	0	N
2	W J	♂	48	170	19	12	0.120	0.134	0.146	0.192	0.154	0	0	0	0	N
3	F H	♂	60	185	20	12	0.098	0.146	0.148	0.121	0.102	0	0	0	0	AP
4	K M	♂	61	195	21	12	0.096	0.126	0.148	0.176	0.114	0	0	0	0	A
5	F A	♂	59	202	23	12	0.102	0.128	0.162	0.184	0.110	0	0	0	0	A
6	W R	♂	51	212	24	12	0.104	0.132	0.168	0.174	0.152	0	0	0	0	A
7	K R	♂	47	186	22	13	0.100	0.154	0.148	0.114	0.100	0	0	0	0	N
8	P J	♂	60	192	22	13	0.112	0.148	0.148	0.110	0.110	0	0	0	0	N
9	F L	♂	61	194	26	13	0.110	0.152	0.156	0.124	0.112	0	0	0	0	N
10	G H	♂	66	220	26	13	0.121	0.162	0.184	0.148	0.134	0	0	0	0	A
11	W I	♂	54	159	20	14	0.114	0.142	0.176	0.125	0.102	0	0	0	0	A
12	K M	♂	54	218	28	15	0.104	0.136	0.148	0.120	0.114	0	0	0	0	N
13	S L	♂	68	186	44	16	0.111	0.146	0.158	0.122	0.100	0	0	0	0	N
14	W S	♂	39	212	30	16	0.104	0.152	0.194	0.154	0.112	0	0	0	0	A
15	G J	♂	57	209	34	19	0.120	0.152	0.150	0.112	0.110	0	0	0	0	N
16	T R	♂	57	186	32	20	0.160	0.240	0.246	0.200	0.150	0	0	0	0	A
17	W T	♂	59	185	33	20	0.142	0.196	0.220	0.212	0.148	0	0	0	0	A
18	S F	♂	58	222	37	20	0.124	0.260	0.245	0.250	0.134	0	0	0	0	A
19	W B	♂	63	200	36	22	0.095	0.150	0.144	0.110	0.100	0	0	0	0	N
20	K L	♂	54	178	32	22	0.112	0.148	0.198	0.210	0.124	0	0	0	0	A
21	J T	♂	62	204	39	23	0.142	0.154	0.184	0.284	0.292	0	0	0	0	AP
22	M O	♂	71	186	40	27	0.148	0.194	0.182	0.146	0.140	0	0	0	0	A
23	N F	♂	68	194	44	29	0.152	0.182	0.195	0.172	0.153	0	0	0	0	A
24	B C	♂	52	205	48	30	0.124	0.168	0.174	0.182	0.148	0	0	0	0	A
25	K R	♂	56	212	50	30	0.114	0.152	0.164	0.188	0.158	0	0	0	0	A
26	T F	♂	59	172	42	32	0.098	0.150	0.144	0.124	0.110	0	0	0	0	N
27	O L	♂	65	192	49	34	0.124	0.184	0.216	0.175	0.122	0	0	0	0	A
28	P O	♂	75	172	46	36	0.116	0.168	0.184	0.170	0.112	0	0	0	0	A
29	F M	♂	69	186	50	36	0.109	0.178	0.176	0.162	0.118	0	0	0	0	A
30	J K	♂	59	192	52	37	0.120	0.154	0.186	0.180	0.134	0	0	0	0	A
31	T B	♂	62	168	48	40	0.138	0.186	0.198	0.216	0.202	0	0	0	0	AP
32	P S	♂	58	216	70	40	0.096	0.146	0.148	0.132	0.112	0	0	0	0	N
33	M K	♂	68	205	60	41	0.126	0.184	0.188	0.170	0.134	0	0	0	0	A
34	F T	♂	54	225	70	45	0.162	0.198	0.214	0.284	0.218	0	0	0	0	AP
35	S L	♂	58	175	56	47	0.098	0.168	0.184	0.188	0.130	0	0	0	0	A
36	B P	♂	53	179	58	48	0.112	0.134	0.146	0.144	0.100	0	0	0	0	N
37	S F	♂	74	204	67	48	0.128	0.138	0.186	0.180	0.132	0	0	0	0	A
38	N D	♂	67	220	72	48	0.122	0.164	0.198	0.192	0.148	0	0	0	0	A
39	W C	♂	59	228	74	48	0.144	0.188	0.222	0.254	0.298	0	0	0	0	AP
40	J F	♂	70	182	63	53	0.114	0.148	0.136	0.132	0.102	0	0	0	0	N
41	B M	♂	71	192	68	54	0.148	0.158	0.198	0.220	0.210	0	0	0	0	AP
42	K T	♂	62	178	67	60	0.154	0.194	0.228	0.254	0.216	0	0	0	0	AP
43	F S	♂	60	176	68	61	0.094	0.144	0.140	0.114	0.102	0	0	0	0	N
44	C F	♂	55	198	72	62	0.138	0.182	0.238	0.242	0.224	0	0	0	0	AP
45	K M	♂	66	174	70	67	0.128	0.164	0.232	0.214	0.148	0	0	0	0	A

In this table ♂ indicates male, ♀, female N, normal response, A, abnormal response and AP, prediabetic response

TABLE 4—*Summary of Cases in Table 3, Arranged According to the Percentage of Overweight*

Percentage of Overweight	Number of Patients	Number of Normal Blood Sugar Responses	Number of Abnormal Blood Sugar Responses
10-19	15	8	7
20-29	8	1	7
30-39	7	1	6
40-49	9	2	7
50-59	2	1	1
60-69	4	1	3
Total	45	14	31

While the number of our cases is perhaps too small to warrant definite conclusions, nevertheless when one compares the response to the ingestion of dextrose among our obese Jewish patients with the result obtained by Paullin in his obese patients in general, there appears to be a considerable higher percentage of abnormal responses among the Jews than among persons who were not Jews 68 per cent as compared to 57.6 per cent This variation may be assumed to be further evidence in favor of the theory that there is a greater tendency among obese Jews to a lowered sugar tolerance and, consequently, to diabetes, than among non-Jewish persons

Considerable attention has been directed to the progressive increase in the consumption of sugar during the past years as a factor in the production of obesity and, therefore, of diabetes Riesman²⁴ ascribes the cause of the increase in diabetes to the greater per capita consumption of sugar added to an increase in sedentary habits

According to Taylor,²⁵ 10 per cent of the population of the United States consumes over 4,000 calories daily without the corresponding necessary requirements for this amount, while a similar percentage of active workers consume less than 2,000 calories He concludes that the work of prosperity increases food consumption while the idleness of hard times reduces it

It is probable, as Emerson and Laimore point out, that "among certain racial, economic and age groups, prosperity tends to tempt them into food habits which exaggerate the usual discrepancy between the amount of food intake and the quantity needed for their respective heat, growth, repair and work requirements"

According to Taylor, with the annual addition of 100 pounds of sugar per capita to the other food, 500 calories a day alone are furnished in the average consumption of 3,600 calories of sugar Emerson and Laimore furnish tables to illustrate that the rise or fall in the rate of consumption of sugar in the United States, Great Britain and France is followed by a similar rise or fall in the death rate from diabetes This fact was especially noted during the period of the World War

While it is evident that there is a tendency toward increase in the consumption of sugar, this fact alone cannot account for the increase in the incidence of diabetes The increased consumption of sugar is simply an index to the tendency to the use of food in general far beyond the bodily requirements, this is especially true after middle life

24 Riesman, quoted by Forchheimer *Therapeutics of Internal Diseases*, New York, D Appleton & Company, 1914, p 718

25 Taylor *J Home Economics*, 16 55 (Feb) 1924, *Harvard Economic Review* 2 283 (April) 1924

Taylor²⁶ says that

Since we are consuming 100 pounds of sugar a year as compared with 75 pounds only a few years ago, this means we are consuming less of cereals, meats, fats or oils. When the dietary habits of overweight individuals are scrutinized, it will be observed that sugar is the food stuff gorged by some, starches by others, fats and oils by others, and meats by others. There is evidence tending to show that the level of average total caloric intake has risen, while the level of average physical exertions has declined, the combined result is an increase in average body weight after the age of 40.

Directly speaking, however, the average increase in body weight cannot be attributed to increase in intake of sugar or any other single food stuff. The remedy is not a motivated decrease in the intake of sugar, but rather a revision downward of the total diet after 40 with increase of physical exercise.

TABLE 5—*Relation of Death Rate from Diabetes to the Consumption of Sugar in the United States, Great Britain and France*

Year	Death from Diabetes Rate per 100,000 in the United States	Consumption of Sugar in Pounds per capita in the United States	Death from Diabetes Rate per 100,000 in Great Britain	Consumption of sugar in Pounds per Capita in Great Britain	Death from Diabetes Rate per 100,000 in Paris	Consumption of Sugar in Pounds in France
1900	9.7	66.60	8.6	71.60	17.0	32.49
1901	10.3	69.70	9.1	76.33		
1902	10.4	72.80	8.4	66.47		
1903	11.3	70.90	8.5	60.29		
1904	12.9	75.30	9.3	70.35		
1905	13.0	70.50	9.3	63.34		
1906	13.0	76.10	9.7	69.35		
1907	13.9	77.54	9.7	70.76		
1908	13.9	81.17	10.3	69.49		
1909	14.4	81.80	10.4	72.40		
1910	14.9	81.60	11.0	70.20	18.4	40.41
1911	14.9	79.20	10.6	75.93	16.9	41.09
1912	15.0	81.30	11.1	74.69	17.7	41.46
1913	15.3	85.40	11.8	78.53	16.0	43.84
1914	16.2	84.29	12.2	72.36	14.3	25.86
1915	17.5	83.83	13.2	65.26	13.2	32.83
1916	17.1	79.34	13.2	56.38	13.4	31.68
1917	17.0	78.58	11.3	42.11	13.5	41.07
1918	15.8	73.36	10.6	45.70	9.6	13.28
1919	14.9	85.43	10.5	59.64	10.3	31.11
1920	16.1	86.56	10.0	45.04		39.29

Finally, while it has been pointed out that all evidence indicates a higher incidence of diabetes in the obese, there is, on the other hand, no evidence to prove that obesity is actually due to the abuse of sugar alone, for overweight is as common whether it is produced by the overuse of carbohydrates, of fats or of alcohol.

Table 5, taken from Emerson and Larimore, presents the relation of the death rate from diabetes to the consumption of sugar in the United States, Great Britain and France. It is clearly shown that there is a direct relation between the increase in the death rate from this disease and a rise in the consumption of sugar and vice versa.

CONCLUSIONS

As a result of our observations, as well as of those of Emerson and Anders, the following conclusions may be drawn

1 There has been a marked increase in the death rate and incidence of diabetes in recent years

2 The increase in the incidence of this disease, while it has included persons of all ages, has revealed itself most markedly in women at all ages and in men over 45

3 The incidence of diabetes is proportionately much greater among the Jewish race. This susceptibility has been variously estimated as being from two to four times as frequent as among the rest of the population

4 The cause of the greater susceptibility to this disease has as yet not been altogether satisfactorily established. Among the more frequent explanations given are lack of proper physical exercise, unsuitable dietary habits, undue nervous strain and marked tendency to obesity, following the forty-fifth year of life. Without doubt, obesity plays by far the most important rôle. In this connection, Joslin has called attention to the important fact that the major number of casual factors referred to can actually be explained on the basis of obesity

5 The relation of obesity to diabetes becomes more evident in the study of blood sugar tolerance curves in obese persons. In 57 per cent of Paullin's cases a lowered blood sugar tolerance was noted, and the proportion was 68 per cent in our obese Jewish patients. A certain number of these cases were detected in persons with early cases of diabetes. The variations between Paullin's and our own figures may perhaps be emphasized as further evidence in favor of the theory that there is a greater tendency to diabetes in obese Jews than in persons who are not Jews

6 The increase in the consumption of sugar during the past years has been assumed to be a factor in the production of obesity and, therefore, of diabetes. There is no evidence, however, to prove that the overuse of sugar alone tends to produce this condition. Obesity can be produced as readily by the inordinate use of carbohydrates, fats or alcohol. It is likely that the overuse of food in general, together with lack of proper exercise, has been the most important cause of obesity, and consequently a direct factor favoring the development of diabetes

7 Finally, as a result of these observations, it is apparent that in order to lessen the incidence of diabetes, the dietary habits of persons with a tendency toward obesity should be regulated, and adequate exercise should be instituted. This is especially important in persons past 45, and even more important among the Jewish population

EXPERIMENTAL UREMIA *

EDMUND ANDREWS, M D

CHICAGO

In previous papers,¹ it was shown that diuresis would not occur in animals suffering from acidosis as evidenced by a low alkali reserve (Van Slyke) even under the extreme provocation of the injection of 25 cc of a 5 per cent solution of sodium chloride per kilogram of body weight. The following experiment is illustrative of what happens in more extreme acidosis.

EXPERIMENTS ON DOGS

Sodium chloride in the dosage mentioned was injected for ninety minutes into a dog weighing 17 kilograms. In this experiment the flow of urine lagged far behind the rate of injection, so that when the animal died after two and one-fourth hours, his water balance was 595 cc plus. This failure of diuresis will result from acidosis of various kinds. The types that I have noted as demonstrated in experimental work include (1) starvation acidosis, (2) exhaustion acidosis, (3) acidosis caused by acute respiratory infections, (4) acidosis resulting from the injection of hydrochloric acid through stomach tubes, (5) acidosis following ether anesthesia and (6) acidosis produced by the absorption of the fluid from autogenous edema. The latter will be exemplified in the following experiment.

Early in the work on this subject, one of the dogs had been tied too tightly to the table so that the leather thongs obstructed the circulation of one paw to such an extent that it became edematous. When this constriction was loosened and the paw massaged, there was a sudden cessation in the flow of urine. This was interpreted to mean that there was a pouring out of considerable fluid into the general circulation from tissues in a high degree of asphyxia, and that the resultant acidosis brought about a fixation of all the free water in the body.

Further experiments of this nature showed that this was unquestionably the case. In a previous communication,² it was shown that under a given stimulus the amount of water which it was possible to cause a dog to excrete was directly proportional to the carbon dioxide value (alkali reserve).³ With this in mind, a dog was selected in which

* From the Department of Surgery, University of Illinois.

1 Andrews, E. Water Metabolism I, Arch Int Med **37** 82 (Jan) 1926, Water Metabolism II, Arch Int Med **37** 559 (April) 1926.

2 Andrews, E. (footnote 1, second reference).

3 Van Slyke, D. D., and Cullen, G. E. Studies of Acidosis, J Biol Chem **30** 289 (June) 1917.

the carbon dioxide combining power was 50, and he was injected with 5 per cent sodium chloride at the rate of 25 cc per kilogram of body weight per hour for ninety minutes. Previous experience had shown that such a dog would be dehydrated to the extent of about 55 cc per kilogram of body weight, in accordance with table given in a previous publication. His leg was tied tightly with a leather thong just before the injection was begun and at a point marked "x" in the curve, the

TABLE 1—*Failure of Animal Given Sodium Chloride for Ninety Minutes to Dehydrate*

Time	Intake Sodium Chloride Solution Cc	Urine	Water Balance Cc	Comment
2 35				Injection begun, carbon dioxide 35.
2 45	80	10	Plus 70	
2 55	160	10	Plus 150	
3 05	240	20	Plus 220	
3 15	320	23	Plus 297	Convulsions
3 25	400	35	Plus 365	
3 35	480	40	Plus 440	
3 45	560	50	Plus 510	
3 55	640	60	Plus 580	Injection stopped, chills
4 05	720	62	Plus 658	
4 15		70	Plus 650	Dyspnea, died
4 35		125	Plus 595	
4 50		125	Plus 595	

TABLE 2—*Effects of Leg Tie*

25 cc 5 per cent sodium chloride per kilogram of body weight injected for ninety minutes

Time Minutes	Intake Sodium Chloride Solution Cc	Urine Cc	Water Balance Cc	Temp	Carbon Dioxide	Comment
0					50	Injection begun
10	40	12	28			
20	85	28	57			
30	125	62	63			
40	160	125	35		48	Leg tie loosened
50	200	150	50		38	
60	250	162	88			
70	290	166	124			
80	335	180	155			
90	375	182	193			
100		188	187			
110		189	187			
120		195	180			
130		195	180			
140		197	178			
150		197	178		23.9	

constriction was loosened and the leg vigorously massaged. The result as seen in table 2 was an almost immediate stoppage in the flow of urine. In this case the carbon dioxide fell ten points in eight minutes.

Numerous other experiments have shown that the fall in carbon dioxide value brought about by such constrictions varies between five and fifteen points. The fall is sharp in normal animals in which the danger point is not reached and does not continue, but reaches a maximum in a few minutes and returns rapidly to normal.

The nature of this acidosis was studied exhaustively, and other toxins besides the acid in the tissues could not be demonstrated. About seventy experiments gave negative results. These included transfusion of blood into other animals, injection of blood from edematous legs, injection of filtered edema fluid, extracts of alcohol and ether, filtered ground muscle and skin extracted with salt solution. Amino-acids could not be demonstrated in the fluids in appreciable amounts. Injections of lactic acid, however, gave similar results, and it seems justifiable to conclude that incomplete oxidation of glucose in the tissues was the offending feature. Clausen⁴ has arrived at similar conclusions in the study of acidosis in infants. This substance is rapidly oxidized or reconstituted into higher molecules, and thus the rapid recovery is to be explained.

It is evident that in such an experiment many of the chemical features of uremia have been reproduced artificially. The organism is acid, and hydremia, increased chlorides and suppression of urine occur.

TABLE 3—*Table of Leg Ties**

Time Minutes	No 1	No 2	No 3	No 4	No 5
0	54.2	48.6	47.8	38.0	44.8
5		43.8		38.6	
10	39.0		42.4		
15		44.8	42.6	35.8	39.6
20				40.2	
30	47.8	47.0	43.2		40.6

* Leg released at 0 time and leg massaged vigorously

Therefore the study was continued, but such overwhelmingly large doses were not used. From 15 to 20 cc per kilogram of body weight of a 5 per cent solution of sodium chloride was injected into a large series of animals (forty-seven) in which suppression of urine was brought about by leg ties, and pictures were produced in nearly half of them which were strikingly similar to that of uremic coma, the so-called "Kussmaul picture." These common factors may be grouped as follows:

1. Marked muscular irritability, followed by convulsions and vomiting, later muscular relaxation and death after many hours or days in coma.
2. Rise in blood pressure followed by marked fall in the later stages.
3. Increased respirations and later pronounced air hunger with forced inspirations involving the accessory muscles, and often typical Cheyne-Stokes breathing.
4. Watery polyuria subsiding into an oliguria with albumin, casts and high specific gravity.
5. Occasional extreme hyperpyrexia in the terminal stages.

4. Clausen, S. W. Anhydremic Acidosis due to Lactic Acid, *Am J Dis Child* 29:761 (June) 1925.

- 6 Rise in the nitrogenous elements in the blood
- 7 Terminal edemas
- 8 "Wet brain," edema of the central nervous system
- 9 Disturbed sugar metabolism with terminal glycosurias
- 10 Carbon dioxide progressively lowered
- 11 Absence of any pathologic renal condition indicating acute changes
- 12 Hydremia
- 13 Increase in the blood and tissue chlorides

The data in table 4 cover the clinical features. Shortly after the injection is begun, there are slight fibrillary twitchings of the muscles. A pronounced rise in the blood pressure takes place, it generally rises to over 200 mg of mercury within a short time. Severe clonic convulsions come on rapidly and occur every few minutes, this stage

TABLE 4—*Artificial Uremia*

Male dog weighing 16 kg

Time	Intake	Urine Cc	Albumin	Casts	Specific Gravity	Blood Pressure	Comment
0 min						120	Injection begun
10 min	45	10	0	0	10 15	130	
20 min	90	22	0	0	10 10	120	Muscular twitchings
30 min	135	40	0	0	10 01	110	Leg tie loosened
40 min	180	42	trace	0		170	Convulsions
50 min	225		0	0		200?	Convulsions, dyspnea
60 min	270	45	trace			200?	Violent convulsions, injections stopped
70 min		46	+			200?	Incoordination
80 min			+			200?	Confused, restless
90 min						200?	
2 hrs		50	++	few		180	Drowsy but easily aroused, one convulsion
5 hrs		50				160	Respirations 28, deeper coma
8 hrs		57	+++	few		100	Respirations 30, cannot be aroused
11 hrs			++				
23 hrs		70			10 21	78	Completely comatose, respirations 31, pulse 130
27 hrs		74					Typical Cheyne Stokes respiration 30 second intervals
35 hrs			++	many		50	

generally lasts from one to one and a half hours. Observations of any degree of accuracy on the blood pressure are impossible during this period, but it seems to remain well over 200. Vomiting often accompanies the convulsive stage. Slight stimuli bring on these convulsions.

After from one to two hours there is a period of drowsiness between the convulsions. In some cases there is a lucid interval between the time the convulsions end and the coma begins, and in others convulsions occur in the earlier stages of the coma. In these early stages there is a markedly increased flow of urine which is of low specific gravity and contains no albumin but occasional casts. Several hours after the beginning of the experiment the dog is generally in deep coma, from which he cannot be aroused. There is little or no change in this condition until death, which may occur in from four hours to three days after the beginning of the coma. During the later stages there is a fall

in blood pressure, suppression of urine or extreme oliguria and large amounts of albumin and casts, air hunger is pronounced. The respiration rises to from 30 to 40 and is deep. The accessory muscles of the thorax are brought into play and the alae nasi are active. Cheyne-Stokes respiration is common, and intervals between the groups of breaths may be as long as thirty seconds. The Kussmaul picture is accurate in every detail.

Fever as a terminal phenomenon occurred sporadically in the series. It generally rose from one to two degrees during the convulsive stage, and this rise was maintained until about the end of the period of coma, when a further extreme rise might occur. Temperatures of from 107 to 109 F were usual, but extreme hyperpyrexias were not observed, such as were reported by Woodyatt⁵ (126 F) or myself⁶ (120 F), in severe dehydrations. As a matter of fact, there is an actual lessening in the amount of circulating fluid in the later stages of our experiments, as is shown by the rise in the refractometric index⁷ of the blood at this time (table 8), without doubt this is an element in the case. It seems reasonable, however, to assume that a more important factor is the fixation of all the water in the body in a firm combination with proteins at this stage of the experiment, as the acidosis is extreme. In other words, in spite of an apparent hydremia, all the water in the body is "fixed," and "free" water is totally absent, this "free" water is necessary in order to allow the heat regulating mechanism to function. Under either of these assumptions, the fever can be classed as dehydration fever. If Fischer's⁸ experiments on colloids are accepted, it is clear that the p_H range of the tissues under such circumstances would bring about the fixation of all the free water which an organism could possibly contain, and with a carbon dioxide value as low as 15, many gallons more would be held if it could be introduced into the body. Thus he has shown that if frog's muscle is immersed in 110 cc, it swells 41 per cent, but if it is immersed in 110 cc distilled water plus 0.25 cc tenth normal hydrochloric acid, it swells 51 per cent. This change in reaction is comparable to the physiologic changes and is sufficient to vary the volume 25 per cent (Fischer sec 1, p 80). It is obvious, therefore, that the fixation of fluids in the tissues would be complete with relatively slight degrees of acidosis.

5 Balcar, J. O., Sansum, W. D., and Woodyatt, R. T. Fever and the Water Reserve of the Body, *Arch. Int. Med.* **24** 116 (July) 1919.

6 Andrews, E. Water Metabolism III, Dehydration Fevers, *Arch. Int. Med.* **37** 815 (June) 1926.

7 Reiss, E. R. Der Brechungskoeffizient des Blutserums als Indikator fuer Eiweissgehalt, Inaug., Strassbourg, 1902.

8 Fischer, M. F. Edema and Nephritis, ed. 3, London, John Wiley & Sons, 1921.

PATHOLOGIC CHANGES

Nitrogen—In this series of animals with artificial uremia the non-protein nitrogen (Folin-Wu⁹) averaged 95 mg per hundred cubic centimeters of blood. Haden and Orr¹⁰ examined the blood of 200 normal dogs, and the average nonprotein nitrogen was 30.8 mg. In only 11 per cent was it over 40, and the highest was 78. Even these figures are probably rather high, as the average carbon dioxide (Van Slyke) of the series was 34, and in half of the dogs it was below 40. In the laboratory of the University of Illinois, dogs that are well nourished and in good condition have almost always had carbon dioxide values over 40, so that one is led to conclude that the animals used by Haden and Orr were not in the best of condition. The nonprotein nitrogen content in this series (95 mg) was not as high as one often finds in uremic coma, but it is now generally understood that retention of waste nitrogen is not the cause of the toxemia in uremia. Beaumont and Dodds¹¹ report four cases of typical uremic coma in which the blood urea never rose over 40 mg per hundred cubic centimeters. Hogeneng and Florence¹² have shown that fish will live and thrive in 2 per cent solutions of urea. Folin and Dennis¹³ have found high urea contents in the blood of cats. In 1890, Von Schroeder¹⁴ found 2.6 per cent urea in the blood of the dogfish, these observations were later confirmed by Rodier¹⁵. Dennis¹⁶ showed that in all elasmobranch fishes the urea content of the blood was from 800 to 1,000 mg per hundred cubic centimeters. Fearon¹⁷ says that urea is not toxic in the ordinary sense, and Herter¹⁸ showed that the enormous concentration of 1 per cent is necessary in the blood of mammals before any untoward symptoms developed. In such high percentages, its action is that of disturbing the osmotic equilibrium of the tissues.

9 Folin, O., and Wu, H. A System of Blood Analysis, J Biol Chem **38** 81 (May) 1919

10 Haden, R. L., and Orr, T. G. Chemical Findings in the Blood of the Normal Dog, J Biol Chem **65** 479 (Sept.) 1925

11 Beaumont, G. E., and Dodds, C. E. Recent Advances in Clinical Medicine, London, P. Blakiston's Son & Co., 1924

12 Hogeneng, L., and Florence, G. Bull Soc chem de biol **3** 174, 1921

13 Folin, O., and Dennis, W. J Biol Chem **11** 87, 1912, Folin, O. J Biol Chem **14** 89, 1913

14 Von Schroeder, quoted by Fearon. Physiol Rev **6** 429 (July) 1926

15 Rodier, quoted by Fearon. Physiol Rev **6** 429 (July) 1926

16 Dennis, W. Nonprotein Organic Constituents in the Blood of Marine Fishes, J Biol Chem **54** 693 (Dec.) 1922

17 Fearon, W. R. The Biochemistry of Urea, Physiol Rev **6** 429 (July) 1926

18 Herter, C. A. On Urea in Some of Its Physiological and Pathological Reactions, Johns Hopkins Hosp Rep **9** 617, 1899

The enormous uric acid values¹⁹ often found in the blood in gout are ample proof that it is not toxic in the amounts noted in uremia. More important, however, is the demonstration by Folin²⁰ that uric acid does not accumulate in the blood of nephrectomized dogs.

In view of these facts, it is not surprising that during the short time these experiments were carried on there was not a further increase in the nonprotein nitrogen to the enormous values often seen in uremia. The absence of such an accumulation strengthens the hypothesis that these waste nitrogenous products have little bearing on the subject of uremia. This point will be further discussed under the heading, "Pathologic Changes in the Kidneys."

Edema—Gross edema occurred only twice in the series, which is not surprising in view of the comparatively short duration of the experiments. When one considers, however, that but 2 per cent at most and often less than 1 per cent of water is added to the organism, it is clear that this edema is not simply a matter of superhydration, but that it represents a change in the allocation of water in the tissues. Unfortunately, the gross specimens were not successfully photographed, but photomicrographs of the muscle tissue in the legs showed marked evidence of edema in and about the muscle fibers (fig. 1).

Most of the dogs in the present series showed a marked edema of the lungs clinically in the later stages of the uremia. This was manifested by moist râles and expectoration of large amounts of frothy mucus. Figure 2 is a photomicrograph of such a lung and shows the edema of the walls of the alveoli.

From an examination of table 7 it is clear that much of the protein in the blood has left the vascular system and is in the tissues. Magnus²¹ has previously demonstrated that as much as 28 per cent of the protein might leave the capillaries after injections of salt, although the capillary walls are ordinarily impermeable to protein. He assumed that salt makes them permeable. Elliger and Klein²² have pointed out the importance of protein that has left the vessels in the further binding of the fluid in the production in tissue edema. Table 8 also shows that the chlorides leave the vessels for the tissues in the terminal stages, and one can therefore assume that in the condition under consideration

19 Folin, O., Berglund, H., and Derick, C. The Uric Acid Problem, *J Biol Chem* **60** 361 (June) 1924.

20 Folin, O. The Nonprotein Nitrogen of Blood in Health and Disease, *Physiol Rev* **2** 460 (July) 1922.

21 Magnus, R. Vergleich der diuretischen Wirksamkeit isotonischer Salzloesungen, *Arch f exper Path u Pharmacol* **64** 68 (Aug) 1900.

22 Elliger, H., and Klein, A. F. Quellungdruck der Eiweisskoerper und Diurese, *Arch f exper Path u Pharmacol* **91** 1 (Oct) 1921.

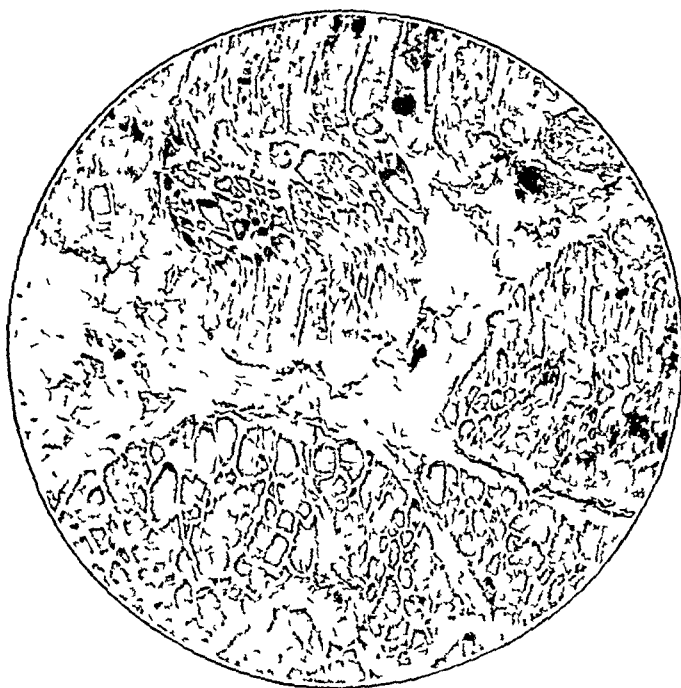


Fig 1—Edema of muscle tissue from the leg, showing separation of fibers and loss of striation



Fig 2—Edema of alveolar walls of the lungs

the greater part of the fluid is no longer in the blood vessels but has made its way into the tissues. The rapidity with which sodium chloride will do this has been well demonstrated by Sherrington and Copeman,²³ who injected one third of the blood volume of 75 per cent sodium chloride during fifteen seconds and drew blood at the end of forty-five seconds. They found that 15 per cent of the injected sodium chloride had already passed into the tissues.

Pathologic Changes in the Brain—Fischer states that many of the clinical phenomena of uremia are due simply to edema of the central nervous system. He showed that an increase of 10 per cent by weight constituted a fatal edema of the brain. Postmortem examination of six

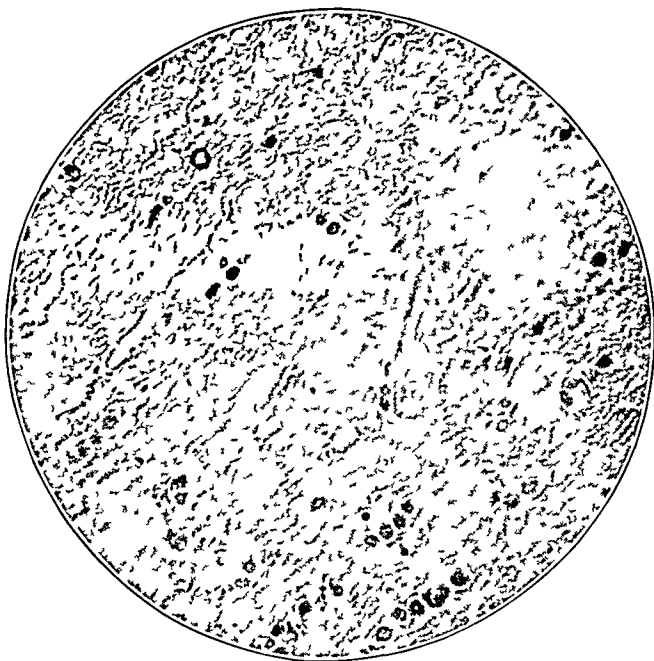


Fig 3—Brain of dog with artificial uremia, showing edema and spreading of fibers of white matter

of the animals in this series showed a typical "wet brain." Figure 3 illustrates the hyperemia of the nervous tissues and the edema in the white substance of the brain causing a separation of the nerve fibers. Attempts were made to study the eyegrounds in these cases, and the characteristic blurring of the outline of the disk and edema hiding the retinal vessels was seen. A diminished intra-ocular tension is characteristic of the later stages of human uremia, and in the animals in this series it was several times so marked that the anterior chamber of the eye was actually collapsed and the cornea concave. Measurements of the intra-ocular tension made by the use of a water manometer

23 Sherrington and Copeman. Blood Volume, J. Physiol. **14** 52, 1893

connected with a needle inserted into the anterior chamber of the eyes of comatose animals showed that the tension had fallen practically to zero. The normal is said to be from 15 to 25 mm (May) ²⁴

Glycosuria—A profound disturbance in the carbohydrate metabolism was noted in all cases that were studied. Several animals had sugar in the last few drops of urine passed. Estimations on the blood sugar and lymph sugar made it clear that had total suppression of urine not been the rule, glycosuria would have been a common occurrence as the urinary threshold was often exceeded. Similar terminal glycosurias are well known in clinical experience, and therefore one is justified in assuming that they are not due to a leaky kidney but to hyperglycemia. Table 5 illustrates this point. In every case there

TABLE 5—*Sugars in Uremia*

Time	Lymph 1	Lymph 2	Lymph 3	Blood (average of 3)
0 Injection Begun	129.6	168.0	97.2	166
10 min	139.6	279.4	94.6	
20 min	133.6		97.2	
30 min	134.6	185.0	92.1	
40 min	125.1	197.8	83.4	127
50 min	175.1	23.4	92.1	
60 min	159.1		92.0	162
70 min	166.9	209.4	89.7	
80 min			94.8	
90 min	159.1	215.9	166.0	204
100 min			112.8	
110 min	175.0	246.0	120.6	
120 min	218.0		126.0	
150 min	331.8	235.0	145.8	193
3 hrs			116.0	
6 hrs				230
18 hrs				210
24 hrs				227
30 hrs				238
36 hrs				140

was a rise in the blood or lymph sugar, and this generally exceeded 200 mg per hundred cubic centimeters. In cases in which enough urine was passed to make a test it contained sugar (table 5).

It had been assumed previously that the reason a patient with nephritis passed sugar in his urine just before he died was that his kidney allowed it to pass. This view is clearly wrong, as hyperglycemia is constant. The explanation of this hyperglycemia is simple. Glycogen stains of sections of the livers of the animals in this series made by the carmine method of Best,²⁵ showed that there was a total absence of glycogen in the later stages, whereas controls showed large amounts of stainable glycogen. In a previous publication ²⁶ it was shown that

24 May, C. H. Diseases of the Eye, New York, William Wood & Co., 1914.

25 Carleton, H. M. Histological Technique, New York, Oxford University Press, 1926, p. 175.

26 Andrews, E. Water Metabolism. IV. Sugar Metabolism in Dehydration, Arch. Int. Med. 38:136 (July) 1926.

hydiemia brought about a washing of glycogen out of the liver. Cajori²⁷ has shown that edema of a muscle blocks its utilization of glucose. Roche and Roche²⁸ also showed that glycolysis would not occur in the presence of marked acidosis. Schiff and Choremis²⁹ found that the hypoglycemia of fasting could be prevented by the administration of fluids. It is evident, therefore, that all the glycogen has been washed out of the liver and at the same time its utilization in the muscles has been prevented when acidosis and edema have been produced, therefore glycogen simply accumulates in the blood.

Acidosis—A progressive fall in carbohydioxide occurs in every case. This happens not only during the injection of chloride but also continues after the injection has been stopped, and the carbon dioxide reaches as low levels as those often seen in uremic coma (table 6). This acidosis is not a feature of the so-called artificial uremia which is brought about by nephrectomy.

TABLE 6—*Acidosis*
Carbon dioxide combining power (Van Slyke)

Time	
0 injection begun	42.8
1 hour injection ended	38.6
2 hours	37.0
3 hours	36.8
6 hours	30.2
11 hours	22.8
22 hours	20.0
25 hours	19.8
31 hours	15.6

Pathologic Changes in the Kidneys—It is well known that one generally cannot correlate the clinical and microscopic pictures in uremia. Evidences of acute exacerbation of nephritis of long standing are usually absent. The changes seen are old, not acute ones causing suppression of urine. Neither suppression of urine alone nor double nephrectomy causes any of the clinical symptoms of uremia. There is, of course, a piling up of nitrogenous waste products in the blood, but never under any circumstances does the clinical picture of uremia arise. After double nephrectomy or ligation of both ureters, dogs live from four to ten days in a practically normal condition. Figure 4 represents a dog five days after double nephrectomy. He was active, played about the laboratory and had a good appetite. Such an animal dies rather

²⁷ Cajori, F. A., Crouter, C. Y., and Pemberton, R. The Effect of Changes in the Circulation on Carbohydrate Utilization, *J. Biol. Chem.* **66**: 89 (Nov.) 1925.

²⁸ Roche and Roche. *pH* Concentration and glycolysis, *Hospitalist* **69**: 1002 (Oct. 14) 1926, abstr. *J. A. M. A.* **88**: 138 (Jan. 8) 1927.

²⁹ Schiff, E., and Choremis, C. Exsiccation and Carbohydrate Metabolism, *Jahrb. f. Kinderh.* **114**: 42 (Sept.) 1926.



Fig 4—Dog five days after double nephrectomy, no signs of uremia

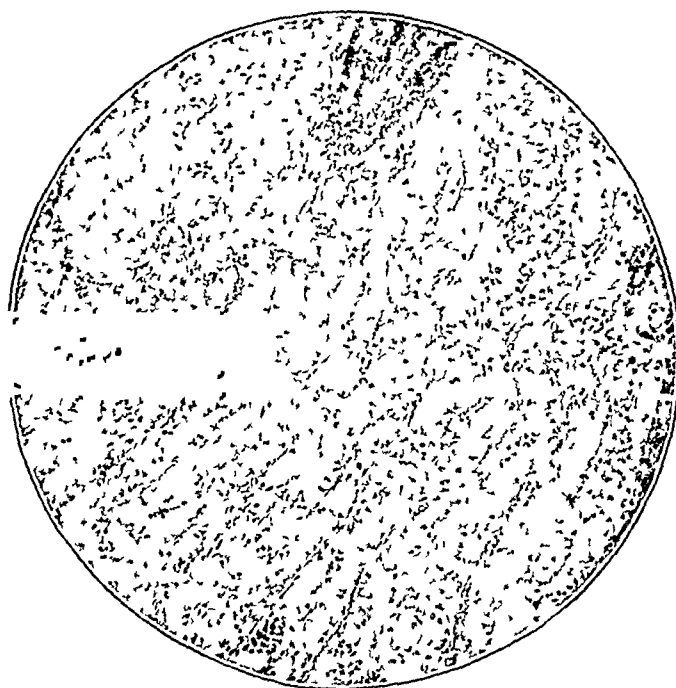


Fig 5—Normal kidney of dog with artificial uremia, showing tubules

suddenly, apparently from inanition, without symptoms such as are ordinarily manifested in the terminal stages of nephritis. Clinical and histologic studies of such animals reveal none of the characteristic changes of uremia except the high nonprotein nitrogen. If, however, such an animal is injected with hypertonic salt solution in sublethal doses, the picture already described is promptly seen. These similarities hold good in the clinical, histologic and chemical changes described in this paper.



Fig 6—Normal kidney of dog with artificial uremia, showing glomerulus under high power magnification

Scarcely any microscopic changes had occurred in the kidneys of the uremic dogs in this series. The glomeruli were invariably normal. The straight tubules and the loops of Henle were normal. Slight changes, certainly falling far short of those necessary to make a diagnosis of nephritis, were noted in the convoluted tubules, they were not extensive enough to cause blocking (figs 5 and 6).

In this series there was a dog with chronic interstitial nephritis (fig 7), and microscopic examination failed to reveal any new changes. Cloudy swelling, edema and glomerular degeneration were conspicuously

absent. These points lend great weight to the opinions of those who believe that the cause of nephritis is to be sought in a general metabolic disturbance and not in the kidneys. In these experiments, at least, it is clear that the kidneys were not responsible for the suppression of urine. The water and salts are fixed in the tissues, and suppression of urine can occur without histologic changes in the kidneys.

These results are in accord with the views already expressed by Fischer, namely, that edema is not due to renal obstruction. The clinical reports of Aldrich and McClure,³⁰ and Aldrich³¹ are strong confirmations of this thesis. By means of the intradermal salt solution

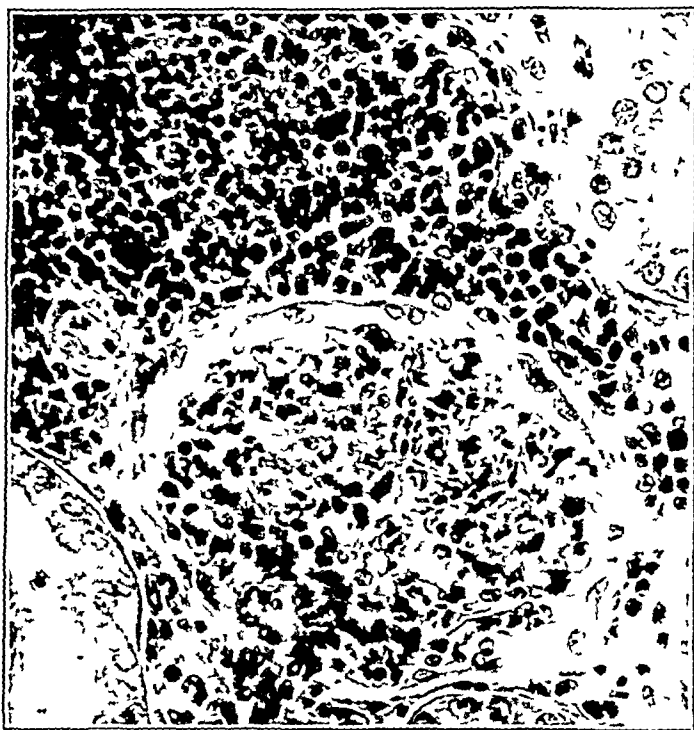


Fig 7—Artificial uremia, produced in old nephritic animal. Changes were all old. There was no cloudy swelling or acute degeneration.

test, they showed clearly that at the end of an attack of acute nephritis, the diuresis did not begin until the tissue thirst had definitely subsided. Aldrich³² expressed similar views and elaborated on the mechanism in a more recent paper. Volhard³³ is also of the opinion that edema is

30 Aldrich, C. A., and McClure, W. B. Time Required for the Disappearance of Intradermally Injected Salt Solution, *J. A. M. A.* **86** 293 (July 28) 1924, The Intradermal Salt Solution Test, *J. A. M. A.* **82** 1425 (May 3) 1924.

31 Aldrich, C. A. The Clinical Course of Generalized Edema, *J. A. M. A.* **84** 481 (Feb 14) 1925.

32 Aldrich, C. A. The Treatment of Nephrosis, *Am. J. Dis. Child.* **33** 163 (Aug) 1926.

33 Volhard, F. *Die doppelseitigen hematologischen Nierenkrankheiten*, Berlin 1918.

not due directly to renal lesions Marriott,³⁴ Clausen³⁵ and many others who have studied the problem recently are in accord on this subject

Water and Chlorides—In the experiment with chlorides, while the injections continued there was a progressive rise both in the water and in the chlorides of the blood, but a fall in both began promptly as soon as the injections ceased (table 7) Table 7 is given to show that these injections did not cause the amount of chlorides in the blood and lymph to rise above the levels found clinically in uremia This is a short experiment in which death occurred rapidly just about the time the amount of blood and lymph chlorides began to fall Table 8 shows what happened in the later stages In this case the suppression of urine was only partial, and relatively little water was added to the organism as a whole The progressive fall in the blood and lymph chlorides after the injections stopped is shown clearly The refracto-

TABLE 7—*Chlorides*

Time Minutes	Intake	Urine	Urine Chlorides	Cl	Blood Sugar	Protein	Lymph Chlorides	Comment
0	0	0	363	437	129	6.2	260	Carbon dioxide 34.5
10	140	20	478	470	135	5.4	285	Injection begun
20	185	68	512	503		5.7	305	
30	225	71	542	477	125	5.1	289	
40	235	73	534	526	175	4.6	319	
50	270	76	537	528	159		322	
60	335	78	517	520	166		315	
70	430	81	538	526			319	
80	525	87		548	159	4.5	332	
90	610			569		4.6	345	Injection stopped
100				607	175	3.4	368	
120				642	218	2.9	389	
130				700	331	2.8	424	Carbon dioxide 15.9
140				670		2.8	406	Died

metric readings and chlorides were taken from another animal, they illustrate how, in the later stages of the experiment, the chlorine made its way out of the blood while water passed from the blood into the tissues and caused anhydremia which probably explains the terminal dehydration fevers in these experiments A count of the red blood cells and estimations on the hemoglobin confirm this Table 9 shows what became of the chlorides It is evident that the liver and brain have the greatest affinity for chlorides This is a constant phenomenon checked many times and to a great extent explains why edema of the central nervous system is often a prominent feature clinically Edema occurs in the brain before it occurs in any other organ, as is evidenced by the clinical phenomena and by the characteristics of the "wet brain" in cases in which edema cannot be demonstrated in other organs

34 Marriott, W. M. Parenchymatous Nephritis in Children, *M. Clin. N. Amer.* 7:1413 (March) 1924.

35 Clausen, S. W. Parenchymatous Nephritis, *Am. J. Dis. Child.* 29:581 (May) 1925.

Pathologic Changes in the Liver—I want to call attention to the most striking pathologic changes noted. As table 9 shows, there was a marked concentration of chlorine in the liver. In the more severe cases a peculiar change in the cells of the liver was found. They appeared to be literally falling to pieces (figs 8 and 9). There was a tremendous swelling of the cells, and the more peripheral portions of the cytoplasm was actually frothy. Myriads of vacuoles were present in the cytoplasm, especially in the outer parts. A striking peculiarity

TABLE 8—*Chlorides*

Time	Intake	Urine		Lymph		Blood *		Comment
		Vol	Chlorides	Ref	Chlorides	Ref	Chlorides	
0						57	513	Carbon dioxide 31.0
10 min	25	3			259			Injection begun
20 min	80							
30 min	130							
40 min	210	24	336		257			
50 min	280	70	507					
60 min	350	137	525		257			
70 min	420	213	554	40.0				
80 min	480	296	553	41.0	269			
90 min	495	352	557	37.5				Injection stopped
100 min		375	623	36.0	352			
110 min		391	617	35.0				
120 min		400	654	35.5	334			
130 min		408	714	34.5	334			
140 min		410	721	32.0	325			
150 min				31.5				
160 min		411	375	29.5	330			
170 min				31.7	305			Carbon dioxide 24.5
180 min				35.5	307			Died
6 hrs						42	814	
12 hrs						47	660	
18 hrs						51	527	

* From similar experiment

TABLE 9—*Chlorides in Organs*

	Controls	Uremic Dogs		72 Hours Cc
		5 Hours Cc	18 Hours Cc	
Blood	513	667	560	520
Muscle	309	338	297	503
Brain	412	462	536	825
Liver	195	338	495	783

is that the nuclei in every case were normal, only the cytoplasm took part in the degenerative changes. The pathologic change in the liver was the only real cellular degeneration that I noted in the experimental animals, and, as I shall attempt to show, was probably intimately connected fundamentally with the cause of the uremic toxemia.

COMMENT

From this series of experiments it is clear that the uremic syndrome in its entirety can be reproduced by the disturbance of the acid-base equilibrium and the mineral salt balance. According to the views of

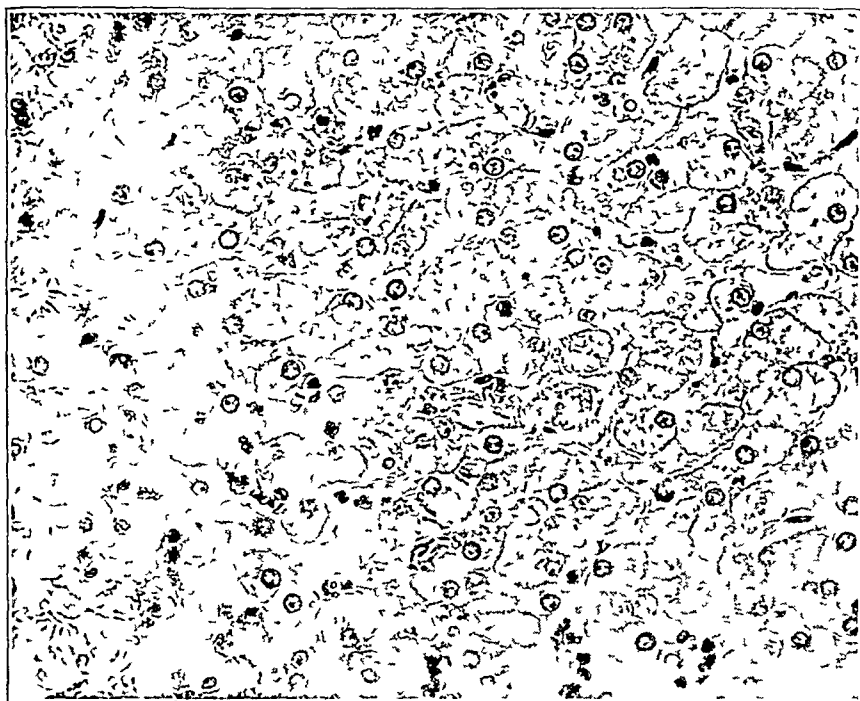


Fig 8—Degenerative changes in liver in artificial uremia under low power magnification

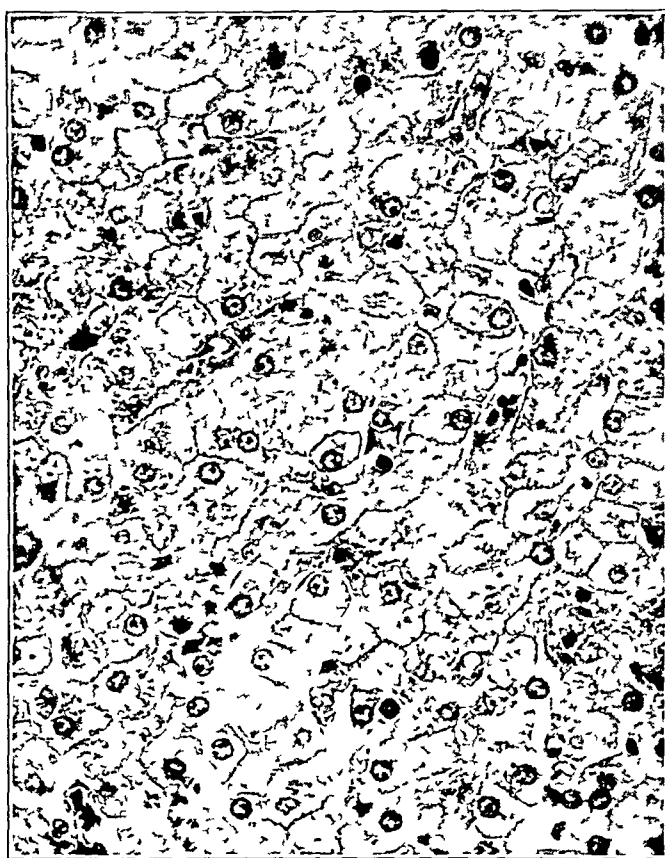


Fig 9—High power magnification of figure 8

Macallum³⁶ and other biologists, life began in water without inorganic salts, and mammalian tissue fluids have the salt content of the Cambrian seas at the time when our ancestors left the sea. The membrane of the cell has developed as a protection against environments with different mineral content, and the nucleus has a membrane which is completely impervious to salts, as Macallum³⁷ has shown that the nucleus is free from inorganic material. This is interesting in view of the fact that in the present experiments the nucleus did not take part in the degenerative process. One is not surprised to find that the commonest disease of mammals, a disease which partakes of the nature of old age, should prove to be a breaking down of the metabolism of inorganic salts. Another interesting point in this connection is the demonstration by Reiss³⁸ that the nucleus of the cell is normal (p_H —7) while the cytoplasm has a p_H of from 5 to 6 due to carbon dioxide.

It has been shown by many workers whose material is well summed up by Hamburger³⁹ and by Jacobs⁴⁰ that this defense is a cell membrane which consists of a layer of emulsion of lipoids in which is contained the greater amount of the mineral salts in the cell. Pascucci⁴¹ has made a membrane artificially by impregnating silk with lecithin and cholesterol and has shown that it would behave in many respects in the same manner as a living membrane. The permeability of this membrane is influenced by the relative concentration of potassium and calcium ions. Loeb⁴² has shown that sodium favors the entrance of potassium ions into the cell. The evidence is now overwhelming that increases in the alkali metals bring about increases in cell permeability. The work of Jacobs, Loeb, Clewes, Harvey, Ostehout, Overton and many others has established this without a doubt. Cases of decreased permeability resulting from calcium are nearly as common. Besides the aforementioned writers, True, Bartlett, Laquer, Rosenow, Magnus and many others have contributed to this field. Hamburger⁴³ has also shown

36 Macallum, A. B. The Palaeochemistry of the Ocean in Relation to Animal and Vegetable Protoplasm, *Tr. Canad. Inst.* **7** 535, 1904.

37 Macallum, A. B. The Palaeochemistry of Body Fluids and Tissues, *Physiol. Rev.* **6** 316 (April) 1926.

38 Reiss, P. Quelques données sur le p_H inférieur apparent du protoplasme et du noyau, *Arch. de phys. biol.* **4** 35, 1924.

39 Hamburger, H. J. A Discourse on Permeability, Physiological and Pathological, *Lancet* **2** 1039 (Nov. 19) 1921.

40 Jacobs, H. M. General Cytology, University of Chicago Press, 1924, p. 99.

41 Pascucci, quoted by Jacobs (footnote 40).

42 Loeb, J. Sodium Chloride and Selective Diffusion in Living Organism, *J. General Physiol.* **5** 231 (Nov.) 1922.

43 Hamburger, R. Ueber die Bedeutung der Kalium- und Calciumionen fuer das kuenstliche Oedem und fuer Gefaessweite, *Biochem. Ztschr.* **129** 153, 1922.

that artificial edema may be produced by solutions deficient in calcium Thomas ⁴⁴ has reproduced this phenomenon in vitro and has shown that the important point is not the concentration of either the potassium or the calcium ion but the relation between the two

It has also been amply demonstrated by the work of Little, Overton, Troendle, Jacobs, Harvey, Bethe and others that increase in the hydrogen ion concentration brings about an increased permeability of cells Of special interest in this connection are the experiments of Koepppe,⁴⁵ who showed that an increase of carbon dioxide rendered cells more permeable to chlorides These observations have been confirmed by Henderson and Spiro ⁴⁶

In view of these facts, it is clear that injections of chlorides into animals that were unable to get rid of them on account of acidosis or nephrectomy must have caused a tremendous increase in the permeability of the cells in the organ which holds the most chlorides, the liver It is even within the range of probability that such an increase of permeability took place that the cells really fell to pieces It has already been shown that the cells were no longer able to retain the carbohydrates which make their way into the blood

The work of Andrews ⁴⁷ and of Hewitt ⁴⁸ has recently called attention to the fact that uremic patients have substances in their blood that give a positive diazo reaction (Ehrlich) Becher ⁴⁹ is of the opinion that these originate in the tissues They probably are partial oxidation products of protein Blotner and Fitz ⁵⁰ confirm these observations, and show that after nephrectomy in dogs, positive diazo reactions can be obtained in from twenty-four to forty-eight hours In the artificial uremia in this series (table 10), while the control nephrectomized animals gave negative reactions throughout, those injected with hypertonic salt solution gave positive reactions within a short time This is probably to be interpreted as a leaking into the circulation of partially oxidized nitrogenous products which are ordinarily held within the cells

44 Thomas, W H Personal communication (work as yet unpublished)

45 Koepppe, H Physiologische Kochsalzloesung, Arch f d ges Physiol **65** 492, 1897

46 Henderson, L J, and Spiro, K Zur Kenntnis des Ionengleichgewichts in Organism Biochem Ztschr **15** 105, 1909

47 Andrews, C H Unexplained Diazo-Colour Reaction in Uremic Sera, Lancet **1** 590 (March 22) 1924

48 Hewitt, L F The Diazo Reaction in Uremic Sera, Biochem J **19** 171 (Feb) 1925

49 Becher, E Diazo and Urochromogen Reactions in Renal Insufficiency, Arch f klin Med **148** 10 (July) 1925

50 Blotner, H, and Fitz, R The Diazo Tests in Nephritis, J A M A **88** 985 (March 26) 1927

The origin of albumin in the urine has as yet not been demonstrated. One is tempted to entertain the possibility that the liver is the source in these cases. It is known that the kidneys are permeable to all proteins except blood proteins. If other proteins are injected intravenously, they are eliminated quantitatively. However, such a condition eventually injures the renal epithelium to such an extent that it becomes permeable to blood proteins as well. In view of the obvious increase in permeability in this case, and especially in view of the fact that it has been demonstrated that the liver allows both carbohydrates and soluble nitrogenous elements to escape, the suggestion that proteins leak from it into the blood seems plausible, the precipitation reactions of these urinary proteins are being studied according to the technic recently published by Welker, Thomas and Hektoen⁵¹

The calcium content of the body cells is difficult to ascertain with any accuracy. Most of the studies on calcium in relation to permeability have been made on lower animals, or indirect methods have been used

TABLE 10—*Diazo Reactions*

Time Hours	Dog A (control)		Dog B		Dog C	
	Diazo	Carbon Dioxide Combining Power	Diazo	Carbon Dioxide	Diazo	Carbon Dioxide
0	0	39.2	0	42.0	0	44.4
1	0		0		0	
2	0		0		positive	35.8
3	0		tr ²	27.2	positive	
4	0		positive		positive	
5	0		positive	died 27.2	positive	died 29.2
8	0	40.3				

* Ureters on 3 dogs ligated at 0 time. Dog A control. Dogs B and C injected with 15 cc, 5 per cent sodium chloride during first hour.

It is known that blood calcium has little relation to the calcium retained in the cell membrane in a protein lipid complex. Injection of large amounts of calcium into the veins is followed by rapid elimination and must often be repeated to maintain a high blood level, and then one is never sure that the calcium is being incorporated into the tissues. The work of Hirschhorn and Maendl⁵² on this phase of the problem leaves us in doubt as to the mechanism of its action. Walters⁵³ and his associates have shown that enormous doses of calcium are necessary to counteract the tendency to hemorrhage in obstructive jaundice, in fact, such large amounts that but infinitesimal proportions of a dose

51 Welker, W. H., Thomas, W. H., and Hektoen, L. Urinary Proteins, *J. A. M. A.* **86** 1333 (May 1) 1926.

52 Hirschhorn, J., and Maendl, H. *Wien Arch. f. inn. Med.* **4** 379, 1922.

53 Walters, W., and Bowler, J. P. The Preoperative Preparation of Patient with Obstructive Jaundice, *Surg. Gynec. Obst.* **69** 200 (Aug.) 1924. Walters, W. Preoperative Preparation of Patients with Obstructive Jaundice, *Minnesota Med.* **6** 25 (Jan.) 1925.

could make its way into the cell. It is clearly a case of application of the law of a mass action. Papers by Blum and others,⁵⁴ Lowenberg⁵⁵ and others, Rockwood and Barrier,⁵⁶ MacCallum,⁵⁷ Porges and Pibram,⁵⁸ and many others have noted the diuretic effects of calcium under certain conditions, especially in some types of edema, but the results are uncertain. Some brilliant results are reported, and in other apparently similar cases the effect is nil. The crux of the matter seems to be the difficulty to distinguish between the "transient" inorganic calcium and the calcium bound up in a protein lipid complex.

Hetenye and Nogradi⁵⁹ have recently demonstrated that in nephritis there is a delay in the excretion of calcium salts. One might assume that in such cases it is needed. All studies in calcium metabolism are handicapped by the fact that calcium is so largely excreted by the bowel, and therefore measured with great difficulty, for that reason, only blood studies made over short periods of time in response to definite stimuli can be of much value. The important studies of Boyd and others⁶⁰ are subject to this criticism. They demonstrated an increase in calcium in the blood of nephritic children and a decrease in potassium. This might be assumed to mean that there was a pouring out of calcium from the tissues into the blood, since further increase of this calcium by injection is of benefit, it is difficult to interpret it any other way.

The experiments of Petersen⁶¹ in anaphylaxis are an excellent example of the method which gives the real answer to the problem. He and his co-workers inserted a cannula into the lymph duct of dogs and measured the calcium produced by the injection of bacterial protein during shock. Their work showed clearly that there was a sharp rise in the calcium and a corresponding fall in the potassium in the lymph,

54 Blum, L., Aubel, E., and Hausknecht, R. L'action diuretique des sels de calcium dans les edemas generales, *Bull et mem Soc med d hop de Par* **2** 1561, 1921.

55 Lowenberg, H. L'action cardiotonique et l'action diuretique du chlorure de calcium, *Ann de med* **13** 172, 1925.

56 Rockwood, R., and Barrier, C. The Calcium Treatment for Edema, *Arch Int Med* **33** 643 (May) 1924.

57 MacCallum, J. B. The Influence of Calcium and Barium on the Secretory Activity of the Kidney, *Univ of Calif Publications (Physiol)* **2** 31, 1904-1905.

58 Porges, O., and Pibram, E. Ueber den Einfluss des Calciums auf Diurese, *Arch f Exper Path u Pharmacol* **59** 30 (June) 1908.

59 Hetenye, G., and Nogradi, S. Calcium Excretion Through the Normal and Diseased Kidney, *Klin Wchnschr* **4** 1308 (July 2) 1925.

60 Boyd, G. L., Courtney, A. M., and MacLachlan, E. The Metabolism of Salts in Nephritis, *Am J Dis Child* **32** 29 (July) 1926. Boyd, G. L., and Courtney, A. M. The Metabolism of Salts in Nephritis, *Am J Dis Child* **32** 197 (Aug) 1926.

61 Petersen, W. F., and Hughes, T. P. Inorganic Alterations of the Lymph in Anaphylactic Shock, *J Biochem* **63** 179 (March) 1925.

which can only be interpreted to mean that the calcium was being disposed of by the cell and the potassium absorbed, which is in complete accord with the known facts of the permeability in such cases. This is the first answer to the question in unequivocal terms. There can be no other interpretation than a fall in the cell calcium and a rise in the cell potassium corresponding to sudden great increase in permeability.

Three such experiments were made on animals in which uremia was induced, and definite results were obtained. The curve in fig 10 shows the average of the three. It is definitely shown that there is a sudden increase in the amount of calcium in the lymph coming from the cells, which are becoming more permeable. This coincides with the injection of sodium chloride.

With these points in view, attempts were made to induce uremia by the injection of Locke's solution, which has the proper calcium-potassium ratio. The syndrome produced was not so severe or prompt in its onset, but nevertheless was typical. With the work of Walters in

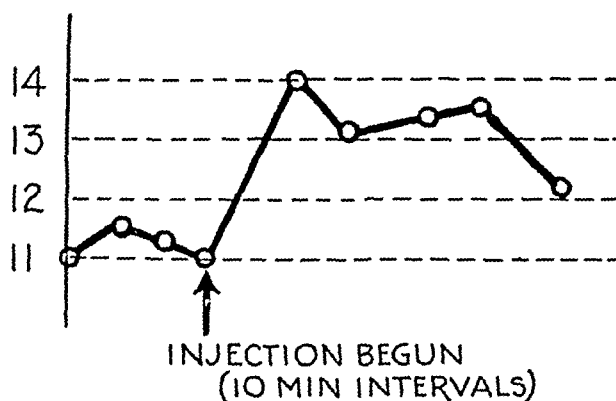


Fig 10—Curve showing average result of injection of calcium in artificial uremia

mind, injections of hypertonic salt were made as before, when the convulsions were at their height and further injections of an overwhelming dose of calcium were given (1 Gm calcium in a dog weighing 8 Kg). The results were surprising. There was a prompt cessation of convulsions, urination began, and the dog made a complete recovery. It is clear that the numerous therapeutic attempts to use calcium have a logical basis, but enormous doses are necessary. It is doubtful whether oral administration can ever be of any value. All the dogs used in the experiments were fed bone ash as a routine, and this did not have any effect. It is the organic calcium which is needed, and overwhelming doses are necessary to bring into play the law of mass action to bring calcium rapidly into cells. The favorable results following the administration of parathyroid extract reported by Mason⁶² are

62 Mason, E. H. A Case of Chronic Nephritis Treated with Collip's Parathyroid Extract, *Canad. M. A. J.* **16** 538 (May) 1926.

suggestive, it is noteworthy that the increase in blood calcium was slight, much less than can be induced by small doses given intravenously, but the increase represents organic calcium and the method is therefore effective

SUMMARY

If animals in which suppression of urine is brought about by either nephrectomy or acidosis are injected with hypertonic salt solution in amounts such that the chloride content of the blood is comparable to that in uremia, they pass into a condition closely resembling uremia. Every manifestation of uremia seen in the human being is reproduced. This is true of the histologic and chemical factors as well. High blood pressure, convulsions followed by coma, "wet brain" and suppression of urine are cardinal points.

Both the chlorides and water rapidly make their way from the blood into the tissues. The brain and liver have the highest chloride contents, and are the organs chiefly involved. There is marked degeneration in the liver which is shown to be due to an increased sodium-calcium ratio which renders the liver cells permeable.

One seems justified in assuming that these degenerative changes in the liver are the fundamental source of the uremic toxins, that albuminous substances are allowed to escape into the blood on account of the destruction of the cell membranes, and that this is the source of the albumin in the urine in nephritis.

CONCLUSIONS

- 1 All the clinical, chemical and histologic features of uremia may be reproduced by disturbing the mineral metabolism, even in the presence of normal kidneys.

- 2 Recent clinical attempts at calcium therapy in nephritis have ample experimental basis, but enormous doses will be needed, and a distinction must be drawn between transient calcium and calcium actually incorporated into the body cells.

Book Reviews

MEMORIAS DO INSTITUTO DE BUTANTAN Volume 1, no 1, 1918, volume 1, no 2, 1918-1919 volume 2, no 1, 1925, volume 3, 1926 Addenda to the Memorias, volume 1, no 1, 1921 São Paulo, Brazil Inst of Butantan

These interesting volumes deal mostly with problems of tropical medicine. Much of the material for the studies is furnished by the poisonous spiders and snakes of the neighborhood of São Paulo. The scientific standards set in this institute of immunology are high. Much of the work consists of careful study and classification of the flora and fauna of the region, and each number contains monographs on the structure and biology of the poisonous snakes. These articles are always lavishly illustrated with drawings, photomicrographs of the poison glands and photographs showing the habits of the snakes. One whole volume (the Addenda) is given to a description of a small snake, *Lachesis*, a close relative of our rattlesnakes, which dwells almost entirely in trees and lives on birds. The venom of this reptile is fatal to birds if injected in amounts as infinitesimal as 0.00001 Gm. An exceedingly powerful antivenom was prepared against this venom.

Volume 1, number 1, is mostly concerned with the flora and fauna of the region, and contains a long article on a genus of insectivorous plants and a series of histologic studies of the poison glands of several species of snakes. These biologic studies are important on account of the great specificity of the antivenoms and the need for rapid diagnosis concerning the source of the lesions clinically. For example, Dr. Vital Brazil, now director of the institute, reports in this number the preparation of a powerful antivenom for scorpion bites. Even in this case its clinical efficiency varied greatly for different species of scorpions.

Volume 1, number 2, is noteworthy on account of an elaborate monograph on filariasis by Dr. Afranio Amaral. The various pathologic conditions are classified, studied and several types of filaria are found. The specificity of these types for different tissues and regions is well marked. A complete series of histories is given with the protozoal observations in each case. Thorough hematologic observations showed that there is a characteristic eosinophilia which is more pronounced during the night and a slight increase of small lymphocytes which becomes much more marked during the night. During the febrile exacerbations, there is a moderate leukocytosis of the polymorphonuclear type.

In considering the therapy of filariasis, one must remember that the first consideration should be directed against the organism. Chemotherapy has been disappointing. The one measure at command is radiotherapy, this has yielded encouraging results, especially in those lesions in which knowledge of the pathologic anatomy is sufficient to indicate to which parts to apply the rays. Surgery is of no avail in the acute stages and, if applied injudiciously, it may be the means of bringing about a dissemination of a localized disease. In those cases in which the filaria are already dead or the process has become stationary, "the cold cases," surgical measures give brilliant results. This is, however, definitely limited to the sequelae of filariasis. In such conditions operations to improve or to anastomose lymph channels (the Kondoleon operation) are generally insufficient per se. In addition, radical excisions of the lymphangiectatic areas are necessary, and the results are good. The tissue healing is surprisingly good in such edematous conditions.

Another interesting contribution in this number is Amaral's report on the healing of phagedenic ulcers under the influence of the local application of dried normal serum. This measure seems to be almost specific in such conditions, it is followed almost overnight by the disappearance of the offending spirochetal flora, and rapid cicatrization takes place. An adequate explanation of this phenomenon can not be found.

Volume 2, number 1, contains a report of the work of Brazil and Vellard on spider venoms, twenty varieties were studied, and specific antiserums were prepared. These are all highly specific, and therefore the recognition of the type of spider is important. The administration of antitoxins not only has the general effect of combating the neurotoxins but acts strongly in preventing or healing the enormous ulcers that result from such bites. The nature of these poisons is unknown, but they have certain peculiarities which sharply distinguish them from most others. They are not entirely destroyed by heat less than 100 C, and they are resistant to the action of chemicals.

Vaz's article on the immunization of animals by mouth against the Shiga bacillus is also well worthy of study.

In conclusion, one is led to regret that the material from this institute is not available in the American literature. Much of our fundamental knowledge of immunology was acquired by study of materials of the class here included, and one can not but feel that future progress will be made by the study of the immunity reactions of these substances which are far simpler than bacterial proteins.

The third volume of the report of the work done by Dr. Vital Brazil and his associates is an imposing one, and covers a wide field of studies in immunology. The major portion of the work, however, deals with the toxicology and biology of the tropical fauna of the neighborhood of São Paulo. The book is liberally illustrated with photographs, some in color.

Among the most noteworthy contributions is the study of Dr. Vellard on toxic secretions from the skin of toads. This interesting material is not a protein, it dries rapidly in air, can be redissolved in distilled water, saline solutions, alcohol, ether and chloroform. It resists without change temperature of 160 degrees, the action of light, time and strong acids and alkalis, with which it gives off color reactions. This substance is exceedingly toxic when introduced either parenterally or orally, it produces nausea and vomiting, followed by paralysis and violent convulsions and death from respiratory failure. The action on the heart is similar to that of digitalis, causing an augmentation of the force of the beat and stoppage in systole.

The previous reports of Vaz on the possibilities of immunization by mouth to the Shiga bacillus are continued and give great hope that this simple method may be of great use as a public health measure. The vaccine is made by killing a twenty-one day culture in bouillon with solution of formaldehyde. A dose of 20 cc. of this vaccine by mouth will completely immunize a rabbit against the development of experimental dysentery.

Next follows a continuation of the studies of the bufo toxin—a complete and elaborate experimental demonstration of the physiologic action of this interesting substance. It is shown to have a markedly exciting action on unstriated muscle tissue, and it can be demonstrated that this is not due to epinephrine content of the secretions as has been suggested by other authors. The third memoir on the toxins of the forms of tarantula found in the neighborhood of the São Paulo is also worthy of mention. There is wide variation in the toxic content of the gland of the various species of the spiders examined, but only two real venoms were found, and against these two exceedingly powerful antitoxin serums are produced which have been demonstrated in a large number of cases to have brilliant clinical results.

BASAL METABOLISM IN HEALTH AND DISEASE, By EUGENE F. DuBois, M.D., Medical Director Russell Sage Institute of Pathology, Associate Professor of Medicine, Cornell University Medical School, New York. Price, \$5. Pp. 431. Philadelphia: Lea & Febiger, 1927.

In this second "thoroughly revised" edition of his book, DuBois states that he attempts to bring basal metabolism out of the realm of pure physiology into the domain of clinical medicine. The attempt is excellent, but the task is not an easy one. "The domain of clinical medicine" is by no

means a simple, homogeneous organization with one aim in view, nor is it easily understood. From the remote rural district to the clinic of a modern medical school is a long way. One cannot read this excellent book without considerable speculation concerning the response it would receive from the various sections of said "domain."

In the first part of the book there is much that is necessarily academic, especially from the standpoint of the clinician, and still he finds here such useful discussions as that in the second chapter, in which the physiology of carbohydrate, fat and protein digestion and the influences of these substances on metabolism are reviewed. Also "the factors which influence the normal basal metabolism" and "theories concerning the basal metabolism" are easily concise contributions to the clinician's daily needs in understanding the task that he attempts in caring for any group of sick people.

The second part of the book deals with metabolism in disease and for one not concerned with the technical side of these studies, it is more interesting and more useful than the first. What physician does not deal with the conditions "undernutrition" and "overnutrition and obesity"? The regulation of weight by appetite, the specific dynamic action of food, endocrine disturbances and the influence of heredity are important subjects considered under the subject of obesity.

In the chapter dealing with metabolism in diabetes the variations encountered are described and, as far as possible, explained. There is careful detail concerning the influence of various arrangements of diet on the metabolism of the diabetic patient. The results obtained by many groups of workers who have concentrated their efforts on this problem are extensively quoted.

There is a timely warning against placing too much emphasis on the metabolic rate alone in the diagnosis of disease of the thyroid. Naturally, the chapter dealing with disease of the thyroid is relatively long. In it is presented a usable summary of the important contributions that have been added to the literature of the subject through studies of metabolism.

The subject of fever is found most interesting and instructive. Here one finds clear discussion, based on quantitative determinations, of many symptoms and factors that are commonplace with clinicians and research workers. Overproduction of heat, diminished elimination of heat, changes that accompany chills and fever, relation of changes in metabolism produced during fever to changes produced by diet, are subjects clearly presented.

There is much else to commend in this book. When one has finished reading it, he feels that it has a definite value for clinician and investigator and that the author has gone far toward accomplishing the purpose described in his preface. It is most appropriate that such a contribution should come from the Russell Sage Institute where so much earnest effort has been made in the study of metabolism.

BIRTH INJURIES OF THE CENTRAL NERVOUS SYSTEM Part 1 Cerebral birth injuries and their results, by F. R. Ford of Johns Hopkins School. Part 2 Obstetrical injuries to the spinal cord by Bronson Crothers and Marion C. Putnam, Harvard Medical School. Price, \$4. Pp. 220, with 70 illustrations. Baltimore: Williams & Wilkins Company, 1927.

Part one deals with the sources of intracranial hemorrhages occurring at birth as coming from (1) the small tentorial vessels, (2) vena magna galeni, which may rupture as the result of distortion during the molding of the head, (3) cerebral veins, namely, the superior longitudinal sinus, (4) in the severe types, from injuries of the superior longitudinal sinus, transverse sinus and straight sinus, (5) but rarely from injury to the choroidal veins, which occurs only in stillborn premature infants.

The author says further that hemorrhage is never extradural, unless associated with fracture of the skull. He also emphasizes the fact that an important contributing cause of intracranial hemorrhage is prematurity. In this con-

nection he quotes authorities who state that intracranial bleeding occurs sixteen times more frequently in premature than in full-term infants. The cutaneous vessels of premature infants are much more fragile. The skin of mature babies will withstand a pressure of 520 mm of mercury while in premature infants a pressure of 150 mm of mercury will cause a hemorrhage of the cutaneous vessels. Another interesting statement by the author is that he has never found a single instance in which a true cerebral diplegia was caused by intracranial hemorrhage at childbirth. A fair percentage of these cases are microcephalic. The paralysis in such cases is a perfect bilateral symmetry in over 95 per cent of the cases and cannot be related to injury at birth or meningeal hemorrhage.

The relation of injury at birth to hydrocephalus, to epilepsy and mental defect, is fairly well discussed, including case histories and anatomic observations.

Part two includes a discussion on injuries to the brachial plexus. The important causal factors as in injuries of the brachial plexus in adults is "traction" and not asphyxia or generalized pressure. The injuries to the plexus and spinal cord in practically all the cases are caused by traction during delivery. The monograph is most interesting and instructive and deserves a place in the library of the general practitioner who must include obstetrics in his practice.

TRAITE DE PHYSIOLOGIE, NORMALE ET PATHOLOGIQUE. Published under the editorship of Drs G. H. Roger and L. Binet, Professors of Physiology in the Faculty of Medicine, University of Paris. Volume 11. Price, 65 francs. Pp 496. Paris: Masson and Cie, 1927.

This volume is a composite production containing chapters on histogenesis of the sex cells, by Champy, sex physiology of the male, by Busquet, sex physiology of the female, by Vignes, secondary sex characters, by Pezard, physiology of pregnancy, by Vignes, physiology of the new-born, by Binet, physiology of lactation, by Porcher, one chapter on histology of growth, by Champy, another chapter on physiology of growth, by Lesne and Binet, and one on heredity and one on teratology, both by Rabaud.

As in similar monographs by several authors, the chapters have an unequal value. The monograph, as a whole, is reliable, helpful, and fairly comprehensive. The chapters by Dr Vignes are particularly excellent. Dr Pezard, who writes on the secondary sex characters, has done much experimental work on the physiology of sex and sex characters, particularly among birds. It is therefore surprising to find that this chapter is not up to date on many points. Dr Pezard seems unfamiliar with the recent important work in this field by Drs Moore and Oslund in this country. The other chapters contain valuable references to the world literature on the specific points under discussion.

The completed series will constitute a valuable work for reference.

THE SPLANCHNOPERIPHERAL BALANCE DURING CHILL AND FEVER¹

WILLIAM F. PETERSEN, M.D.

AND

ERNST F. MÜLLER (HAMBURG)
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Among the principal clinical alterations noted during the onset of acute infections, the chill plays a notable part. By this term is designated a number of phenomena, the most obvious being the muscle tremor and the actual sensory perception of cold by the patient.

The association of the chill with the invasion of the blood stream by bacteria has been so well established ever since the work of Schottmüller¹ that we feel justified in accepting the clinical phenomenon as evidence of blood invasion during an infectious disease. This acceptance of the fact of invasion by no means gives an explanation of the ultimate mechanism involved.

Schottmüller found that the mere presence of bacteria in the blood did not cause a chill. The chill takes place some time after the invasion (from thirty to ninety minutes, depending on the number and type of organism and also on the person involved). From the time of invasion to the time of the chill, the number of culturable organisms rapidly diminishes. The chill takes place when the organisms have made contact with the body cells or when the products of the bacteria have made such contact.

When one examines the skin of a patient in a chill, pallor, pilomotor stimulation, a transient expression of sweat from the sweat glands, together with lowered temperature of the skin are to be observed. This is perceived by the patient and gives the sensory stimulus. The capillaries and the arterioles are contracted. The muscle tremor varies from one hardly perceptible to one of great intensity. The question that arises when one considers this picture is whether these predominantly vascular peripheral phenomena are due to the direct effect of the bacteria or the toxic agent or whether one is dealing with an effect that primarily involves some other organ or organ group and only secondarily brings about manifestations at the periphery. In previous papers, we² have

¹ From the Department of Pathology, University of Illinois College of Medicine.

¹ Schottmüller, H. *München med. Wchnschr.* 58:2051, 1911.

² Müller, E. F., and Petersen, W. F. *Klin. Wchnschr.* 5:52 and 137, 1926.

called attention to the fact that with the injection of bacteria (or of peptone, arsenic, etc.) a profound alteration is brought about in the vasomotor systems of the splanchnic as well as the peripheral areas, with a dilatation of the former and a constriction of the latter. Such diametrically opposite orientation can hardly be due to the direct effect of the same agent on the tissues, i.e., the vascular endothelium or the neurovascular elements. It must be assumed that the characteristic phenomena of the chill are the result of changes initiated when the toxic agent has entered into cellular contact and has there caused changes to which the peripheral vascular reaction is secondary. There are two methods of approach to this problem. In the first place, we know that a change in distribution of the leukocytes³ takes place with changes in the tonus of the peripheral or splanchnic areas. With peripheral sympathetic orientation, a drop in leukocytes is a constant accompaniment and at the same time there is an increase in the number in the splanchnic area. Conversely, there is an increase in the peripheral leukocytes with a parasympathetic orientation.⁴

A peripheral leukopenia is constantly found during the chill. So, too, in experimental animals one can observe a splanchnic leukocytosis at the same time.

We can also make certain deductions from experiments with lymph.⁵ Immediately with the onset of the chill (in experimental animals), a tremendous increase in lymph volume takes place. This lymph contains protein in greater amount than normally. While, presumably, the mere muscle tremor might increase the volume of lymph flow, the lymph that originates in the peripheral regions is relatively poor in protein. The increased flow of a highly concentrated lymph is further evidence that the splanchnic region is in a state of increased metabolic activity.

This increase in splanchnic activity (parasympathetic orientation) during the time of chill is clinically demonstrated in various ways. The contractions of the stomach cease, it dilates and vomiting occurs, the vomiting is the result of the contraction of the abdominal muscles. We rarely fail to observe vomiting in the patient in the pneumonic chill, we find nausea and vomiting frequently in other chills of infectious origin.

3 Muller, E. F. Evidence of Nervous Control of Leukocytic Activity by the Involuntary Nervous System, *Arch Int Med* **37** 268 (Feb) 1926.

4 When we speak of parasympathetic orientation, we do not restrict the term to an organ status induced merely by stimulation of anatomically defined parasympathetic nerves. We regarded it as the state of organ activity in a region of increased metabolism, increased permeability, increased blood flow, increased action currents, etc. We use the term sympathetic to denote the converse of the state, i.e., tissue rest. In a recent paper, Schilf takes a somewhat similar position (*Klin Wchnschr* **6** 193, 1927).

5 Petersen, W. F. Hughes, T. P., Jaffe, R. H., and Levinson, S. A. *J Immunol* **8** 323, 1923.

and occasionally after injections of vaccine. Naturally, the absence of nausea is not indicative of an absent parasympathetic effect on the stomach. Practically every intravenous injection (aisphenamine, peptone, bacteria) is followed by some dilatation of the stomach, the intensity varying in different persons and under different conditions.⁶

It may be permissible in passing to point out the interrelation of the skin and the splanchnic phenomena in shock after perforation, with acute pancreatitis, and acute peritonitis, in general. Every insult to the peritoneum—an ordinary laparotomy, etc.—leads to a distribution leukopenia, i.e., to an alteration of the splanchnoperipheral balance. In the case of perforation, the prompt reorientation of both regions (with peripheral sympathetic and splanchnic parasympathetic fixation) is so pronounced that one speaks of a peculiar "facies" as more or less pathognomonic. In the fully developed peritonitis, this fixation of the balance is most pronounced, and a constant nausea and vomiting are associated with a continued "facies peritonealis."

According to the so-called Dastie-Morat law, the concentration of the blood in the splanchnic area with a paralysis of the vasomotor system in this region (as assumed for shock) is balanced by a peripheral depletion of blood. This is not true, because if we sever the vasomotor nerves to an extremity, it does not lose its blood content under such conditions. At the stage of the chill, no paralysis of the splanchnic area occurs, on the contrary, one deals with a profound stimulation—two conditions that are different in character. In the chill the splanchnoperipheral balance, which under normal conditions is in a constant state of coordinating adjustment of the one region to the other, has become "fixed," and both regions are still oppositely oriented, but no longer adjust the balance to minor physiologic demands.

The effect of this fixation immediately becomes apparent in the change in the temperature of the body, coincident to or following on the rigor. So intimately are the two connected that it is the common assumption of clinicians as well as physiologists that the increase in temperature in part is due to the muscle tremor.

We have pointed out that during the time of the chill an increased production of lymph takes place from the splanchnic region. Increased production of lymph is associated with increased activity of the organs (parasympathetic status) and with this increased activity an increased metabolic rate and production of heat are naturally associated (Asher). Of the splanchnic organs, the liver is chiefly concerned. All measurable functions of the liver indicate its greatly augmented activity during the chill. We have, for instance, measured the output of bile and of biliary

⁶ Petersen, W. F., and Muller, E. F. *Proc Soc Exper Biol & Med* **24** 155, 1926.

pigments both in the patient and in experimental animals. Such an animal experiment is shown in dog 85 (chart 1). Jaffe⁷ has recently shown that during the chill the reticulo-endothelium of the liver takes out fat from the circulation of the blood in one half the time normally required.

The increase in permeability of the capillaries and cells of the liver associated with this increase in activity is made evident in the more rapid passage of injected hemoglobin from the blood stream to the lymph during shock, as well as the fact that bile pigment enters the lymph stream.⁸

For the intestine, Arnold and King⁹ have demonstrated that one of the first symptoms of shock (before a fall in blood pressure takes place) is a tremendous increase in the flow of secretion into the lumen. For three splanchnic organs, the stomach, intestines and liver, one has then the right to assume greatly increased metabolic activity and production of heat.

But why should the toxic agent (the bacteria in this case) cause an increase in the function of the splanchnic area and a decrease in the function of the peripheral organs? For the obvious reason that every foreign body (formed and probably unformed) is promptly taken out of the circulation by the splanchnic reticulo-endothelium and there concentrated. This results in an immediate stimulation of this system of cells—a stimulation transmitted to their immediate neighbors, the organs of the region (liver, spleen, intestine, etc.). The splanchnic region is fixed in a parasympathetic state. The periphery is fixed sympathetically with diminished function. The direction of the orientation is still normal, only the intensity has been altered, and because of the intensity, minor regulatory fluctuations are no longer apparent. Fever now results because the increased heat produced in the splanchnic area cannot be dissipated by a periphery which is in a state of arrest. The phenomena at the periphery, which are so obviously striking, are merely secondary in character.

With this concept in mind, we can understand the vicious circle under which the splanchnic region particularly labors. The organ that is functioning at an augmented rate is much more permeable than a resting organ. The splanchnic region will therefore be selectively injured to a greater extent by further toxic material than will the rest of the body. Pathologically, the effects of this are seen in the parenchymal injury grossly apparent in every patient who has died from an acute infection or intoxication.

It is chiefly the reaction of the liver with which we are concerned when bacteriemia takes place. The peripheral reaction which has given

7 Jaffe, R. H. Personal communication to the author.

8 Petersen, W. F., and Levinson, S. A. *J. Immunol.* **8** 349, 1923.

9 King, C. E., and Arnold, Lloyd. *Am. J. Physiol.* **59** 97, 1922.

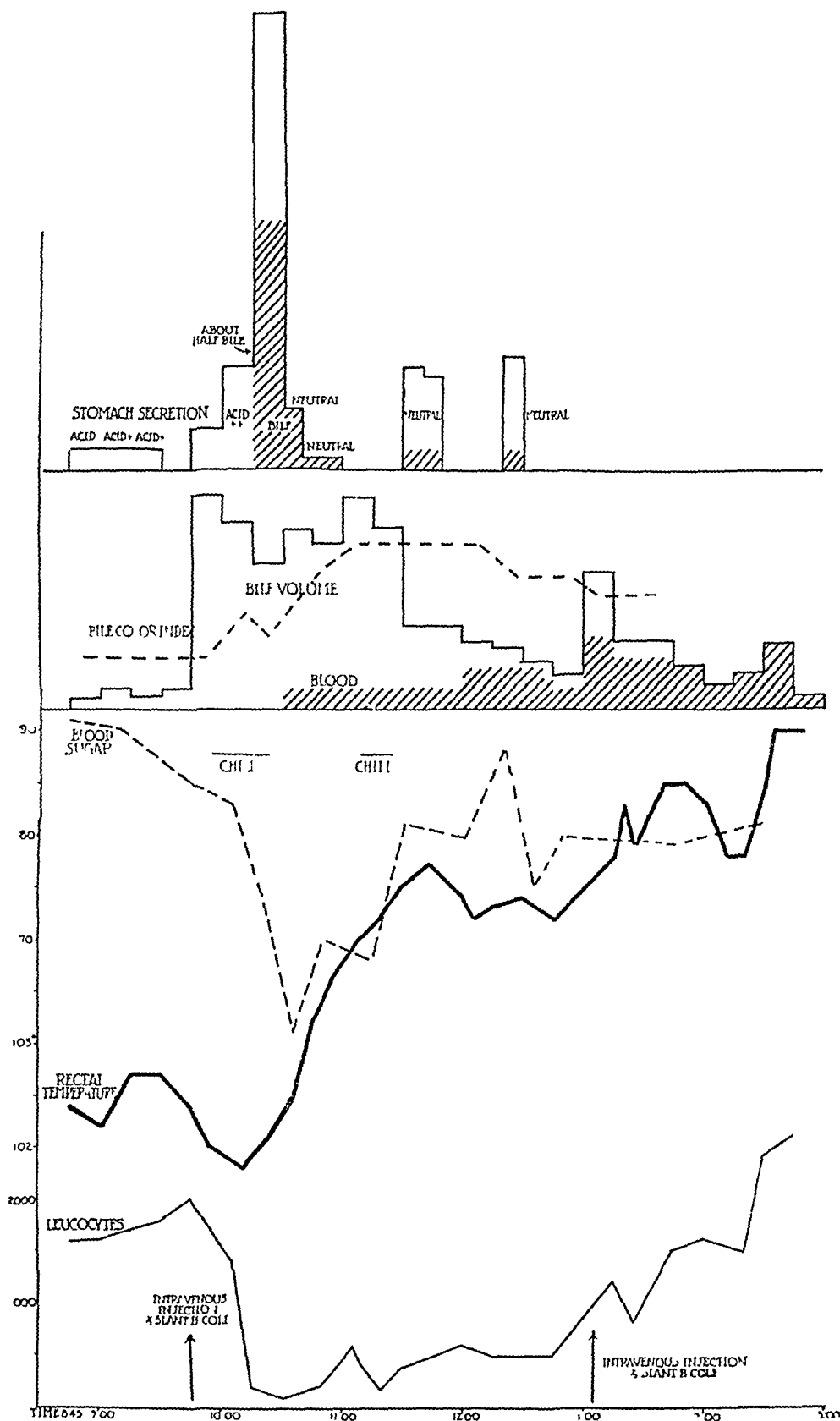


Chart 1—Effect of two intravenous injections of *B. coli* (1% slant) on gastric secretion and bile flow with relation to chill. Normal dog with duodenal fistula.

the entire phenomenon its name is merely the expression of the vegetative compensation vital to the organism in preserving its functional equilibrium. It is a maximal, unidirectional fixation of a tonus normally labile.

We should not omit from these introductory remarks a brief consideration of the so-called thermoregulatory center of the midbrain, and its importance for the splanchnoperipheral equilibrium. We know that the periphery and the splanchnic area are antagonistically oriented under normal conditions and that this condition prevails as long as the vegetative nerve tracts are intact. We have shown¹⁰ that the most trivial stimulation of either of the organ systems is followed by antagonistic reactions of the other group (distribution of leukocytes, analysis of the lymph, etc.). We know, too, that minor cellular stimulation (irradiation of the skin, digestive activity of the gastro-intestinal tract) will bring about changes in this regulatory mechanism. Temperature and sugar puncture into the midbrain bring about disturbances antagonistic in orientation in the two major regions, just as well as the bacteriemia that produces the chill.

Whether a direct effect of bacteria or bacterial products directly affects nerve elements of a temperature¹¹ center cannot be determined clinically. We do know, however, that pronounced stimulation of either the splanchnic or the peripheral region will lead to changes in the balance, comparable, even if not so intense, as if toxic substances have actually been injected into the blood stream. The intensity of the effect in the antagonistic group of organs will depend on the intensity of the operative stimulus. It is at least probable that with intense stimulation of the skin one can exclude the direct effect of toxic substances on the temperature center. The effects of emotion in at least affecting the stability of the reactions are not to be excluded from consideration.

Every alteration of the cellular activity of an organ, if sufficiently intensive, produces alteration in the vegetative nervous system. However, it seems improbable, as the response is always similar and as the intensity of the response varies only with the stimulus, that in one instance vegetative reorientation will depend on a direct effect of the agent (bacteria or toxic products) on a presumptive thermoregulatory center, while in another instance (physiologic activity-digestion, etc.) it is mediated remotely and indirectly wholly through impulses that travel via the nervous system.

That impulses reach some regulatory center, wherever it may be located, seems probable. Whether such a "center" is pictured as a

10 Petersen and von Oettingen, W. F. *Arch f exper Path u Pharmakol* 123 160 1927

11 The discussion by Toenneissen is perhaps as complete as might be desired. In Muller, L. R. *Die Lebensnerven*, ed 2, Berlin, 1924, p 471.

nucleus in the midbrain, or is regarded as an inherent and widely diffused property of the vegetative nervous system with its functioning dependent only on undisturbed continuity of the entire system, is immaterial. It is only of moment to keep in mind that if an alteration in the balance can be initiated by a stimuli originating in some part of the system (during which entrance of bacteria and intoxicating products into the blood stream can be excluded), then presumably such an alteration of the balance can occur even when bacteria are circulating in the blood stream. This is the more likely, since it is known that they may be circulating for some time without effect and may only produce the phenomena of chill and fever when they have been engulfed, not in the central nervous system but in the liver and splanchnic area.

MUSCLE TREMOR

As stated in the beginning, the muscle tremor occupies the center of clinical interest, for with its sudden onset it overshadows all associated phenomena. The interpretation of this reaction and the relation to other organ phenomena involved offers so many difficulties that a clinical analysis may seem justified.

The muscle rigor is independent of volition. It does not depend on central innervation. This fact itself is of the utmost importance. The tremor persists when the motor nerves have been severed. The tremor cannot be inhibited by will even with intact innervation. Involuntarily induced by some agent closely associated with the underlying noxious cause, it represents a muscle reaction differing greatly from the normal.

The tremor is furthermore characterized clinically by another phenomenon, namely, that it is practically inexhaustible in duration and degree. Even the cachectic and exhausted patient will react in his twentieth chill with the same intensity and vigor and will have as severe tremor hour after hour as at the onset of the infection. Indeed, we know from clinical experience that a fatal sepsis will be characterized by chills in which the terminal severity of the reaction is augmented in duration and intensity. True, the chill and rigor are associated with a feeling of fatigue which, however, begins at the onset of the tremor, continues throughout its course and may actually seem lessened to the patient after cessation of the tremor. This occurs despite the actual feeling of lassitude after the chill has passed. It is of importance to keep in mind that no diminution in the intensity of the reaction takes place despite the feeling of fatigue. We shall show later that actually a lowering of muscular power takes place during the rigor. Perhaps even the rigor associated with the application of external cold should be considered here. The effect of intense cold on the untrained skin is associated with so-called "goose-flesh," a contraction of the

arterioles and capillaries, a lowering of the cellular permeability and a diminution in the elimination of heat and water from the skin. The tremor, too, is involuntary, is not associated with effects of objective fatigue and is to be regarded as a reaction to a definite and unusual stimulus. But the tremor is readily overcome when voluntary motor impulses supervene, and thereby differs from the chill of an infection. This might indicate that the fundamental alteration which takes place with muscle tremor on external application of cold may be similar in character to that which takes place during the chill of infection, the difference being in the intensity of the process rather than in its character.

We must take into consideration the peculiar tremor of the exophthalmic patient, the tremor of fatigue and the tremor following injections of epinephrine. In all these cases, the movement of the muscles is involuntary, in the exophthalmic case it is often initiated or intensified by voluntary motion, but not under voluntary control. It may be present for long periods of time. Here, too, it is practically not subject to fatigue, despite the fact that it is associated with the sensation of fatigue on the part of the patient and even with evidence of actual muscular weakness. We have merely brought these conditions into discussions to illustrate the fact that while such muscular tremor does not occur normally, related phenomena on the part of the voluntary muscles are by no means unknown in pathologic conditions not due to infection.

The two most pronounced muscular phenomena during a chill are first, the tremor, and second, the diminution in functional capacity. We must examine these two phenomena in order to arrive at some conclusion as to what the phenomenon involves. The matter of functional capacity will be examined first. If a muscle is contracted by voluntary impulse the bundles are shortened, and with it there is found an increase in metabolic activity, with increase in size of the individual elements and increased permeability. Autonomically, an increase in the size of the capillary bed that supplies the muscle group takes place. It is of importance to keep in mind the experiments of Weizsacher¹² and Hill, which have demonstrated that the increase in metabolism takes place after the contraction. If the tremor of a chill is simulated voluntarily in the muscle, one can clinically demonstrate an increase in volume, in temperature and in vascularization. In the extremity under observation one can furthermore determine first an imperceptible, later an apparent, increase in the secretion of sweat, as evidence of the participation of the skin in the vegetative reorientation. In other words, one deals with a coordinated and paralleling functional increase of tissue activity both centrally and vegetatively controlled.

12 Weizsacher, V. J. Physiol. 48: 396, 1914.

If the patient is now asked during a chill to execute some voluntary movement, he will usually respond that it is impossible for him to do so, if he does, there is a total absence of increase in volume, there is no increase in warmth, no circulatory response, and no secretion of sweat. All of this merely indicates that under such conditions the normal vegetative responses have been totally suppressed despite the intact voluntary nervous connections.

These normal vegetative reactions which occur simultaneously with the onset of voluntary nervous stimuli are probably truly autonomous, originating locally as reflexes. They are not wholly dependent on the motor innervation nor on the connection with higher vegetative centers. Even after the sympathetic connections are severed, they remain intact.

Clinically, these characteristic alterations in muscle functions during a chill are well known. If one has the opportunity to observe a young, previously healthy adult who is suddenly seized with a chill, one is struck with the prompt loss of muscular strength. Strong workmen can hardly lift a light weight, even locomotion is attended with difficulty. This is the crucial difference between the feeling of loss of power which is immediately incident to the onset of a chill and which persists during its duration, and the fatigue which becomes apparent after long continued normal muscular effort. The muscle in rigor becomes functionally disabled along with the feeling of fatigue. This status is immediately initiated with the onset of the tremor. Despite the feeling of fatigue and actual diminution in power, the tremor persists for hours without diminution. The normally working muscle fatigues to a degree commensurate with the degree and duration of the work performed.

The conclusion is reached that loss of muscular power during chill does not depend on fatigue as such, but on an inhibition of the normal vegetative correlation, that is, on the ability of the vascular bed to dilate. This inhibition is due to impulses which persist during the period of the chill.

This change in the reactivity of the skeletal musculature during chill, evident in its loss of functional power, is indicative of a transient "sympathetic" inhibitory effect.

The experiments of Cannon have made it probable that with the onset of an insult such as that offered by the continuous injection of bacteria, epinephrine is promptly augmented in the circulation¹³ as it is too, with chilling and with work (Hartman, and Hartman, Waite and Polwee¹⁴) and possibly in exophthalmic goiter—all closely related in their form of muscular tremor.

13 Cannon W. B. *Bodily Changes in Pain*, New York 1915.

14 Hartman, F. A., and Hartman, W. B. *Am. J. Physiol.* **65** 612 1923.
Hartman, F. A., Waite, R. H., and Powell, E. F. *Am. J. Physiol.* **60** 255 1922.

In this connection, we cannot avoid a brief discussion of the present status of the rôle of the sympathetic nerves on skeletal muscle. It has been established anatomically that sympathetic fibers are plentifully supplied to the muscles but that their function is undetermined. The work of Hunter and Royle¹⁵ took the interest from the academic field to that of the clinic, and clinical failure led to the assumption that the sympathetic function was negligible. Indeed, the recent work of Porter¹⁶ and Ransom and Hinsey¹⁷ might lend support to such a view. On the other hand we cannot discount much evidence to the contrary. Thus Freudenberg¹⁸ and Brehme and Popoviciu's¹⁹ observations that in an existing alkalosis the injection of epinephrine will bring about the onset of tetany (with or without the exclusion of the motor innervation) would make a peripheral effect of the epinephrine probable.

Undoubtedly, the work of Orbeli, reviewed recently by Brucke²⁰ as well as by Fulton,²¹ is convincing in character. Orbeli has shown that sympathetic stimulation definitely increases the tone of fatigued muscle. In ischemic tetanized muscle, sympathetic stimulation not only increased the tone but delayed the fatigue effects which were normally apparent. The effect of the increased tonus so produced probably overcompensates any negative inotropic effects due to a concomitant vasoconstriction, such as would be implied in Wastl's experiments.²² Fulton, in his review, considers it "desirable simply to recognize that the sympathetic system does influence the action of the skeletal muscle."

Additional evidence has recently been presented by Hartman.²³ When observing skeletal muscle directly under the microscope, he found that small doses of epinephrine were followed by vascular dilatation and larger doses, by constriction of the arterioles and venules of the muscle tissue. A distinct change in the field of observation was noted in that with epinephrine the whole field became brighter, while with narcosis the reverse was observed. In addition, a distinct transverse tremor of the muscle was noted, which was present even after the motor nerves were cut.

Associated is the change in the type of reaction of the muscle which also speaks for a reaction differing from the normal. If we ask a patient during the bacterial chill to execute a complex voluntary move-

15 Hunter, J. I., and Royle, N. D. *Surg Gynec Obst* **39** 701 and 721, 1924

16 Porter, E. L. *Am J Physiol* **78** 495, 1926

17 Ransom, S. W., and Hinsey, J. C. *J Comp Neurol* **42** 69, 1926

18 Freudenberg, E. *Klin Wchnschr* **6** 634, 1927

19 Brehme, T., and Popoviciu, G. *Ztschr f d ges exper Med* **52** 579, 1926

20 Brucke, E. T. *Klin Wchnschr* **6** 703, 1927

21 Fulton, J. F. *Muscular Contraction*, Baltimore, Williams & Wilkins, 1926

22 Wastl, H. *J Physiol* **60** 109, 1925

23 Hartman, F. A. *Am Physiol Soc*, Rochester, N. Y., 1927

ment, the tremor persists despite the superimposed central impulse (as it does, too, with the tremor of fatigue, chill and exophthalmic goiter.) Voluntary impulse and involuntary tremor probably are based on two wholly different phenomena if they can so exist side by side.

In the tremor accompanying external cold, voluntary movements rapidly terminate the involuntary tremor, giving further evidence that voluntary motion and involuntary tremor rest on a different basis and act differently on the muscle. The fact that here a sufficiently powerful voluntary impulse will suppress the involuntary tremor would indicate merely a difference in degree rather than in fundamental cause.

From purely clinical reasoning, it seems probable that the tremor of the chill is associated with unusual autonomic or chemical conditions, more or less antagonistic to the ordinary voluntary movement, and that it represents not muscle function in the usual sense but merely a different state of the muscle. The fact that such a muscle does not increase in size, does not become fatigued and does not become warm during the course of the movement is further evidence in the same direction.

Obviously, we might seek to explain the peculiar tremor on the basis of a clonus. With vasoconstriction, we may assume an increase in acid metabolites and with it an increase in the threshold of excitability and a diminution in the size of the action current of the individual fiber. We know that the sense of fatigue is an immediate accompaniment of the bacterial chill. Presumably, the increase in acid metabolites may affect the motor endplate, more probably, it may affect the reaction of the muscle fiber itself, such a fatigued fiber acting more slowly and developing much less tension than a normal fiber.²⁴

The vasoconstriction and the lowering of the temperature may involve a change in the excitability of the proprioceptive nerve endings, resulting in a typical clonic response in a muscle under increased tonus when synchronous proprioceptive stimuli may be operative.

As a matter of fact, the trembling muscle gives little or no evidence of what is commonly accepted as muscular work. The quivering is actually clonic in character and is not ordinary muscular contraction. Older theories of the regulation of temperature accepted this tremor and muscular work as equivalent, but one must not be blinded to the probability that wholly different phenomena may be present.

The fact that the chill following the external application of cold begins involuntarily and cannot be voluntarily suppressed brings up a related condition in which the voluntary muscle is also "out of bounds," if we may use that expression. Such a condition occurs in deep hypnosis, and the work of von Grafe²⁵ and others shows that the muscular

²⁴ Fulton (footnote 21, p. 195)

²⁵ Von Grafe, E. *Deutsche Zeitschrift für Nervenheilkunde* **79** 359, 1923

metabolism sinks on such functional deletion of impulses, the active current is diminished and the muscle may even assume a cataleptic rigidity

Such rigidity represents shortening without consumption of energy, i e., a state similar to that studied by Noyons and von Uexkuell, which they termed "muscle blockade" ²⁶ As this would lead too far afield and is not essential for the problem at hand, we shall not enter further into the theoretical side of the question

Even when we are dealing with tonically contracting muscle, there may be actual evidence of diminished metabolic processes (galvanometric determinations Foix and Thevenard,²⁷ Lewy,²⁸ Golla²⁹ and Wertheim-Solomonson³⁰) These observers reach the conclusion that in muscular contraction one must distinguish two mechanisms, the one a fixation without increase in metabolism, the other the common voluntary muscular contraction The first mechanism presumably would involve the sarcoplasm, which Roberts³¹ assumes may contract with great efficiency, i e., without extensive production of heat

Clinically, it is of importance to know that (1) we may have a condition of muscular shortening independent of voluntary control, during which the muscular metabolism is diminished This state, which is seen in cataleptic rigidity, represents a condition during which the muscle gets along with less than the normal metabolic exchange³² (2) At the opposite extreme is the voluntary functioning muscle, with increased metabolism, in which the increase in metabolic processes presumably takes place between individual contractions of individual fibers The vegetative activity (vasodilatation) increases and diminishes with increase or decrease in function (3) The resting state described by Meyerhoff represents muscle respiration in the normal condition between these two extremes

In the rigor we seem to deal with skeletal muscle which differs on the one hand from the permanent cataleptic shortening and on the other from normal muscular contraction There is reason to believe that there is increased tonus due to sympathetic stimulation (central and periph-

26 Noyons and von Uexkuell *Ztschr f Biol* **56** 139, 1911

27 Foix, C, and Thevenard, A *J de physiol et de path gen* **23** 332 1925

28 Lewy F H *Die Lehre vom Tonus und des Bewegung*, Berlin, Julius Springer, 1923

29 Golla, F L *Lancet* **2** 115, 1921

30 Wertheim-Solomonson, J K A *Brain* **43** 369, 1920

31 Roberts F *Brain* **39** 297 1916

32 Janet Clark's recently reported experiment might offer another explanation of long continued muscular shortening without work Crystal Fiber Diffraction Patterns from Relaxed and Contracted Muscles, meeting of the Am Physiol Soc Rochester N Y, 1927

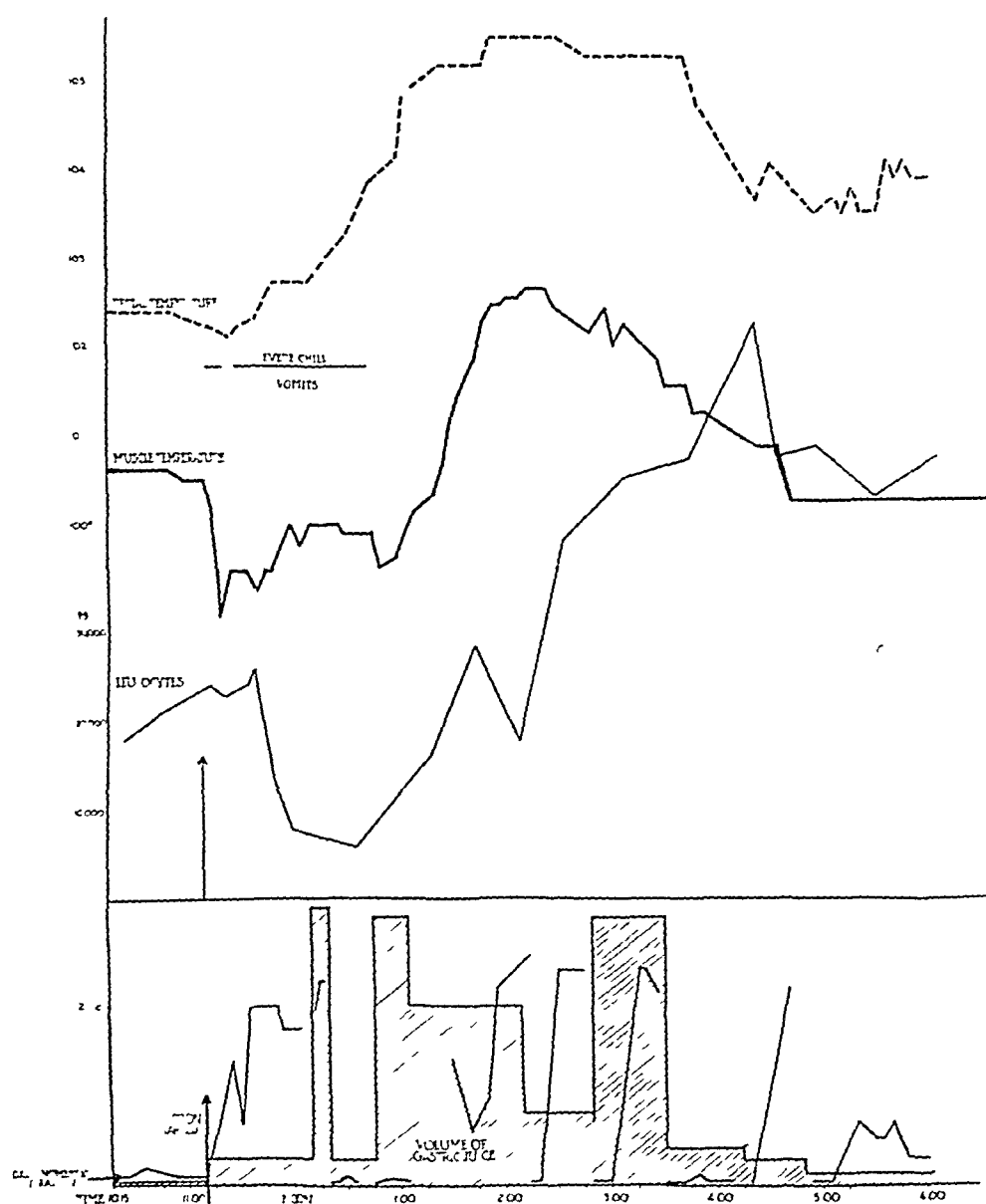


Chart 2—Comparison of muscle and rectal temperatures during bacterial chill (effect on peripheral leukocyte count and gastric secretion included) In this experiment as in others of the series, normal dogs were used without general anesthesia. Local anesthesia was used as required. Continuous injection of a suspension of *B. coli* (1 slant to 500 cc saline solution) was made intravenously with the Woodyatt pump. It will be noted that during the time of the chill the muscle temperature drops and remains lower than during the control period for two hours, while the rectal temperature has increased 2.5 F. A considerable increase in volume of gastric juice was noted, and galvanometric titration, according to the method of Unger (*Arch f. Verdauungskr.* **37**), with the electrode in the intact stomach indicated a great increase in gastric acidity.

eral) and that an intense constriction of the arterioles and capillaries takes place with a resulting accumulation of metabolites. These may put the individual fiber into the status of fatigue with great reduction of the tensile effort. They probably change the threshold of proprioceptive stimuli, and by summation and synchronism, the muscle fibers not being shortened, an actual clonus may supervene. There is experimental reason to believe that this need not be associated with increased metabolic activity.

Certainly, autonomic effects become apparent which seemingly are diametrically opposite to those usually associated with working muscle. In the cataleptic state, previously latent sympathetic forces, normally overshadowed by voluntary control, are suddenly dominant, in the rigor, the previously normal autonomic apparatus is suddenly augmented so that the apparent phenomena may overbalance powerful voluntary impulses and dominate the picture. The rigor is not a permanent contraction, such as is found in the cataleptic state, but is a relatively slow and incoordinated shortening of individual fibers. In the cataleptic person, we have no longer voluntary impulse but autonomic fixation or blockade, with unchanging status. The rigor offers a different picture. Motor impulses are still possible, but the sympathetic fixation is so great that the normal vegetative reflexes which would normally bring about coincident vasodilatation are held in abeyance.

EXPERIMENTS

These clinical considerations seemed to us sufficiently attractive to invite investigation in animals, as the direct measurement of actual production of local heat in the muscles is not readily carried out in the patient. For our purpose we have made use of simple methods using unanesthetized normal dogs as experimental animals and reproducing the clinical picture as far as possible by a continuous injection of small amounts of suspensions of living *B. coli* (approximately 4 or 5 million organisms per cubic centimeter, and injecting approximately 1 cc per minute with the Woodyatt pump. Muscle and rectal temperature were recorded both by means of accurate clinical thermometers as well as by delicate electrical thermocouples. In addition, observations of the lymph were made together with constant leukocyte counts, control of blood chemistry, etc.

By means of such injections a close approximation to the normal human chill can be obtained. This is initiated about thirty minutes after the onset of the injection and may persist for varying periods of time. In every experiment in which a demonstrable chill was to be observed, no increase in muscle temperature was found, despite a sharp increase in rectal temperature during the same interval of time. Com-

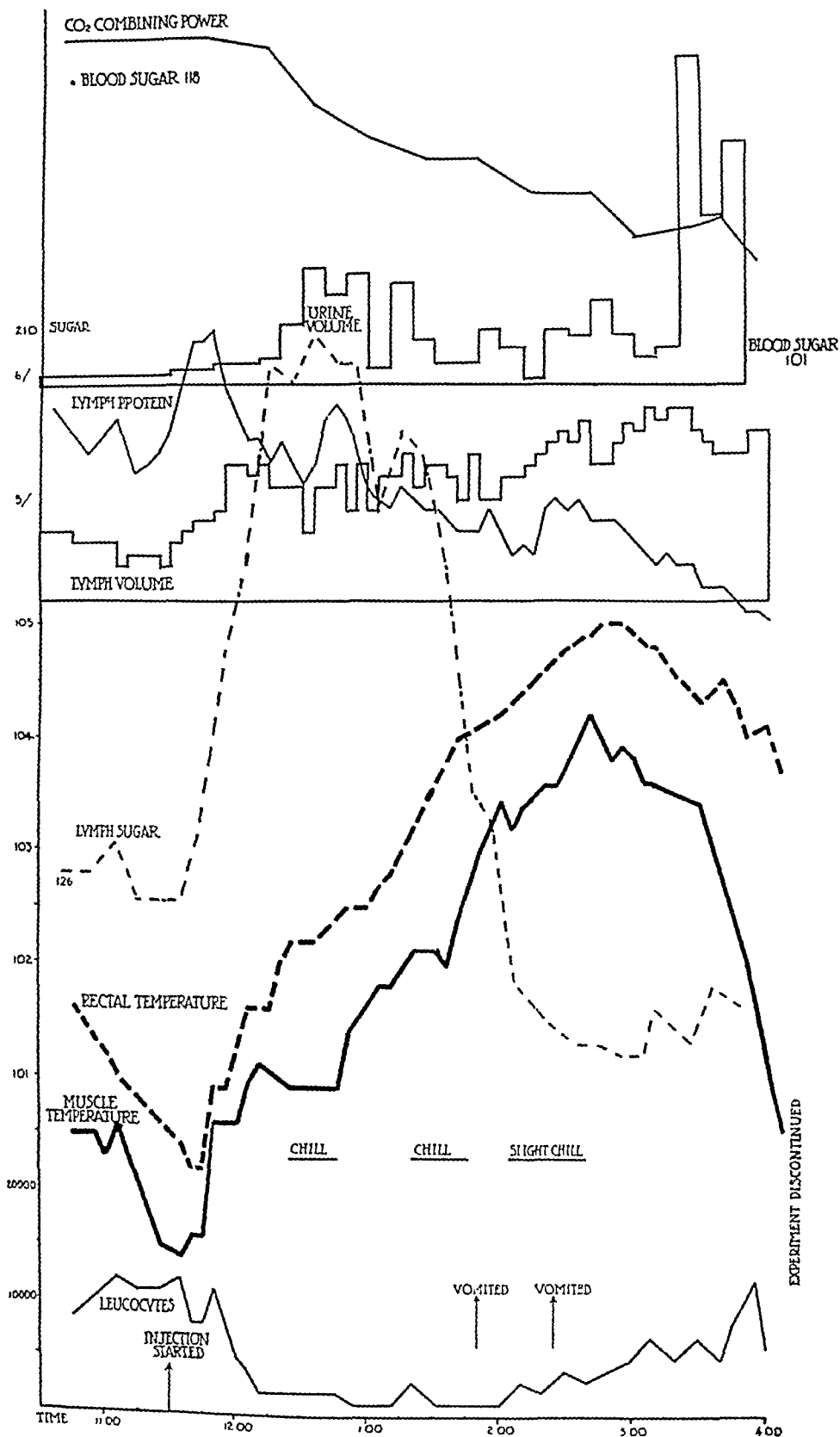


Chart 3—Comparison of muscle and rectal temperatures during bacterial chill. Continuous injection of *B. coli*, with graph illustrating the effects on the lymph volume, sugar and protein and the carbon dioxide combining power, urine volume and leukocyte count. These reactions are typical of the results in experiments of this character. It will be noted that each time a perceptible muscular chill was observed, the muscle temperature was diminished, while the rectal temperature increased without marked retardation.

parable increase was noted in the liver, although this temperature was usually higher than that of the rectum. Frequently, an actual diminution in muscle temperature takes place during the time of the rigor, while the rectal temperature increases. As Du Bois has shown, this occurs when there is actually no increase in the rate of the peripheral heat loss.

Only at the end of the chill, and usually when a coincident increase in the peripheral leukocytes would indicate some vasodilatation in the periphery, will an abrupt increase in temperature of the muscles be observed. We can only conclude that during rigor, with shortening of the muscle, no increase in the production of heat takes place. And if, despite an increase in the temperature of the rest of the body, delay occurs in the warming of the muscles, it can be due only to a fixation of the autonomic status in the muscle which prevents the dilatation of the capillaries and the arterioles.

This seems analogous to the state that is found in the skin. The fact that the capillaries of the skin bleed poorly during a chill is readily observed. The lack of the heat inflow to the muscles takes origin in the same phenomenon that prevents bleeding from the patient in the cataleptic or the hypnotic state when pricked by a needle. Just as the hypnotic patient bleeds from the needle wound after the release of the suggestion, so the muscles, after the rigor, are rapidly warmed to the temperature of the internal organs.

COMMENT

Every phenomenon in the disease picture represents merely one phase of the deviation from the normal and should be considered, therefore, merely as a single stone in the larger mosaic. It might seem permissible, therefore, to discuss the phenomenon of chill in its relation to the changes in other organs.

During chill, we are dealing with an organism in which a profound alteration of large groups of organs has taken place autonomically, that is, irrespective of the type of causative agent, the chill expresses tremendous functional stimulation of the splanchnic region, with a partial or total arrest of the peripheral functions. For the skin, we know that loss of heat is reduced to a minimum when the contraction of the peripheral vascular system takes place. The dependence of this condition on the sympathetic tonus has been established, and that a sudden release of epinephrine from the suprarenal gland is associated seems probable (Cannon¹³). The proof that similar phenomena dominate the musculature during the chill extends the present concept to the largest of the peripheral regions. Skin, muscle and peripheral vascular system act as a unit in the response to the altered conditions of the body.

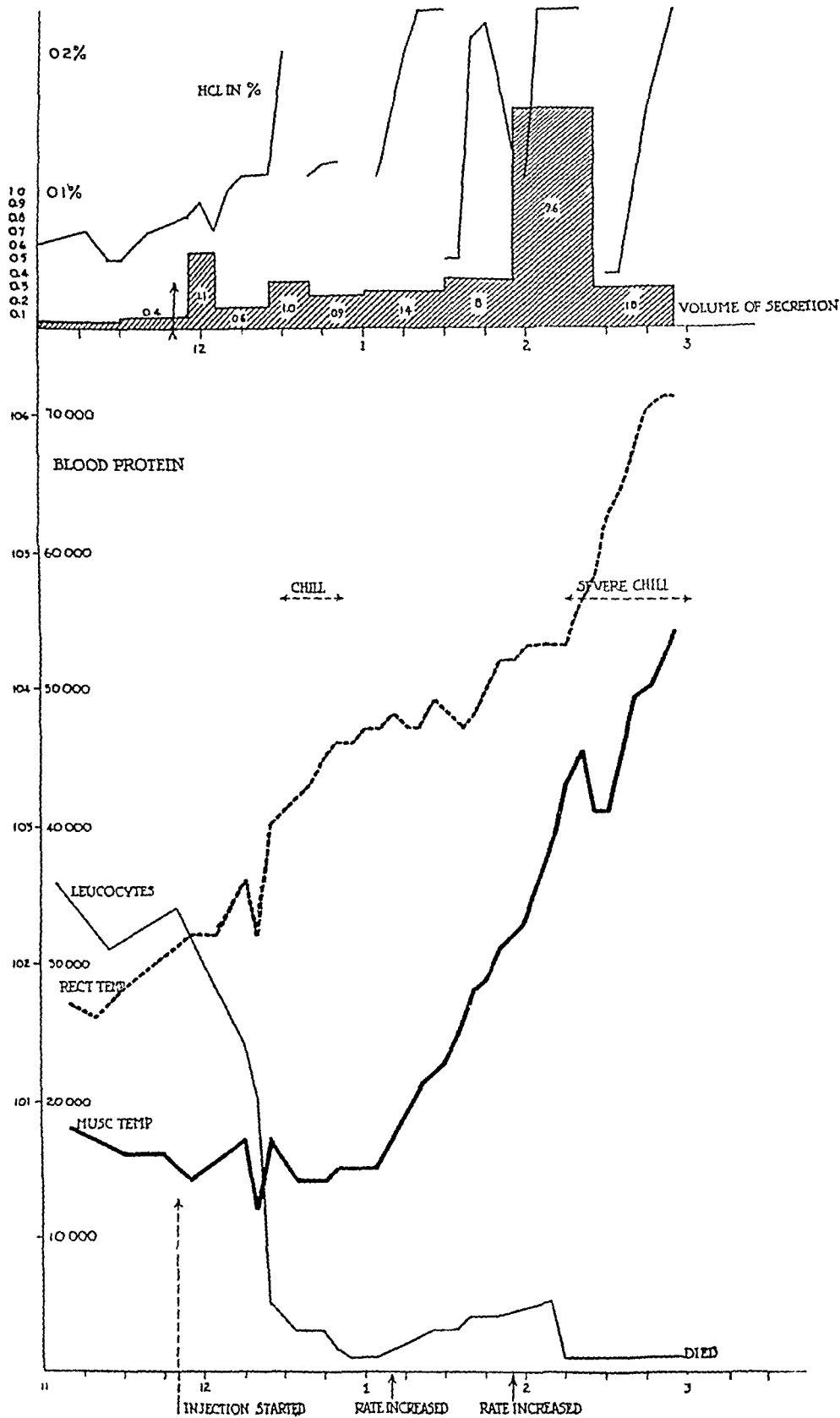


Chart 4—Comparison of muscle and rectal temperatures during bacterial chill. Continuous injection of *B. coli* (285 cc in all) in dog with gastrostomy. It will be observed that the rectal temperature increased about 20 F in the hour after the injection was commenced, while the temperature of the muscles remained low during the time of chill, later (at 2:30 p.m.) with a second chill, the temperature of the muscles diminished while the rectal temperature increased. The typical effect on the gastric secretion and acidity is to be noted.

Recently, Cannon and his associates³³ have begun a study of regulation of heat and have emphasized particularly the rôle of the release of epinephrine. They, too, seem of the opinion that equilibration by means of muscle shivering and the presumptive warming of the body by such means are relatively negligible factors as contrasted to the increase in metabolism induced by the flooding of the organisms by epinephrine, and the production of heat without any muscular activity at all.

Our interpretation differs in the fundamental assumption that the two regions (splanchnic and peripheral) are oppositely oriented. The intense stimulation of the splanchnic area with its great increase in permeability gives no evidence of the effect of the epinephrine in the ordinary sense, despite the fact that epinephrine is probably present in greater amount in the circulation. This need not be surprising as epinephrine under such conditions may give a paradoxical effect, i.e., it may augment the parasympathetic status. Thus, under such conditions, it does not contract the musculature of the arterioles nor present symptoms of shock.

Muscle tremor, whenever apparent, has usually been accepted as synonymous with the production of heat, such as takes place with voluntary contraction of the muscles. It is generally assumed that the increase in temperature following the rigor is due, in part at least, to heat so engendered. Our experiments indicate, on the contrary, that the chill produced in the dog by the continuous injection of colon bacilli is always associated with an increase in the splanchnic activity, indeed, it probably is to be regarded as produced by this splanchnic orientation. During this time, the abdominal temperature is rising. The association of the increase in splanchnic activity with the tremor of the muscle in shock (whether bacterial, or due to external cold) is so constant that one may assume the splanchnic stimulation when he observes the tremor of the muscles. On the other hand, not every increase in splanchnic activity results in tremor of the muscle. Presumably, the latter takes place only when the autonomic rearrangement reaches a certain degree of intensity.

In the fixation of the balance, it is to be remembered that the condition in the periphery can be maintained practically indefinitely, but the status in the splanchnic area will be self limited, the period of stimulation leading either to a (1) reversal, or (2) to fatigue and ultimately to death of the cells. We will describe the chemical basis of these changes in other papers.

The tremor of the muscles may be assumed, therefore, to indicate increase in splanchnic activity and production of internal heat. Conversely, the increase in splanchnic activity, if of sufficient intensity, will

³³ Cannon, W. B., Querido, A., Britton, S. W., and Bright, E. M. *Am J Physiol* **79** 466, 1927.

produce tremor of the muscles. The tremor need not appear, the increase in temperature may take place gradually without the intense autonomic fixation apparent in chill. This is the more common status in the ordinary fever.

The question of the increase in metabolism and its relation to the muscular activity is one that can hardly be answered clinically. While it would be of interest to determine the exact oxygen exchange in the muscle during tremor, for our clinical purpose it is sufficient to establish the fact that the increase in temperature does not come from muscular work in the ordinary sense.

CONCLUSIONS

The production of bacterial chill and fever is the result of the fixation of the splanchnoperipheral autonomic balance. The entrance of bacteria into the blood stream is followed by their fixation by the reticulo-endothelial elements of the splanchnic area. This (depending on the toxicity of the organisms) is followed by a marked stimulation of these cells and of the organs in which they occur—liver, spleen, bone-marrow and gastro-intestinal system. This stimulation involves a parasympathetic status of the organ group and with it a sympathetic orientation of the peripheral organs. In this peripheral group, the muscles are oriented in the same direction as the skin and vascular tissues. The intense sympathetic orientation, which arrests the activity and restricts the blood supply, is an adaptation to the fundamental alterations in the condition of existence of the whole organism. The muscle tremor itself is the expression of the intense sympathetic orientation, augmented to such a degree that it cannot be overcome by will, as is still possible in the chill accompanying the external application of cold.

The tremor itself, presumably a clonic effect in muscle with increased tonus, may be associated with local effect of metabolic products accumulated when vascular constriction takes place, rather than a phenomenon due to the mere deprivation of oxygen. The tremor is not associated with increased production of heat and is to be regarded as a phenomenon analogous to that studied in smooth muscle during so-called "muscle blockade."

THE MONOCYTES IN PNEUMONIA

A CLINICAL AND HEMATOLOGIC STUDY *

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NEW YORK

An attempt was made recently to compare and to contrast the changes in the leukocyte counts in patients with bronchopneumonia and with suppuration. It was noted that in the cases of bronchopneumonia the monocytes in the circulating blood increased in the early stages of the disease to a point definitely above normal, and that later the number¹ again became normal.

The object of the present work was to determine whether similar changes occurred in patients with lobar pneumonia and, by comparing the changing blood picture with the clinical course of the disease, to determine whether any deductions could be drawn regarding the function of these cells.

Daily total leukocyte counts were performed on the patients, the blood being obtained by pricking the lobe of the ear. Cover-glass films of the blood were made at the same time and stained. The differential blood count was performed under the oil immersion lens. In more than half the cases studied, the percentage of each type of cell was determined by counting 500 successive cells seen in the film. In the remainder, a pair of cover-glass films were stained, and 100 cells were examined in each. When the total leukocyte count was high, 400 or 500 cells were counted in these cases also. The total number of each type of cell per cubic millimeter was calculated from the total leukocyte count and from the percentages. These numbers were plotted in the forms of graphs, so that a picture was obtained of the changes in numbers in each type of cell during the course of the disease.

In the great majority of instances, the monocyte is easily recognized. It is distinct in type from the other two main groups, the polymorphonuclears and the lymphocytes. It has been recognized as a distinct type of cell for many years. When well stained with one of the Romanowsky stains, it presents, briefly, the following characteristics. The basichromatin of the nucleus lies in fine strands, so that the lighter staining portions of the nucleus appear to lie close together. These light staining portions are evenly distributed through the nucleus, in this it contrasts with the nucleus of the lymphocyte in which the light staining portions lie far apart and are unevenly distributed, owing to the

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coarse structure of the basichromatin masses in the lymphocyte. The cytoplasm of the monocyte stains a cloudy blue, different from the clear blue cytoplasm of the lymphocyte. In this cloudy blue cytoplasm are seen immense numbers of evenly distributed fine granules, which stain a brighter color than do the neutrophil granules of a polymorphonuclear. These granules are distinct from the much larger bright red globular bodies frequently seen in the clear cytoplasm of a lymphocyte. This description corresponds to the monocyte of Naegeli's classification.² It has been called a large mononuclear leukocyte or transitional cell in other classifications.

In normal blood the monocytes comprise about from 2 to 6 per cent of the total number of leukocytes. In total numbers 500 or 600 monocytes per cubic millimeter is probably the maximum normal.

REACTION OF MONOCYTES IN CIRCULATING BLOOD

The main part of this work consists in daily observations on twenty cases of lobar pneumonia. The only method of selection adopted was that patients were used on whom the first blood examination could be performed within three days of the onset of the disease. In all cases the onset was sufficiently characteristic so that the day of disease on which the first examination was made was known with fair certainty. Throughout the paper, when a certain day is mentioned in connection with any case, it refers to the day of the disease, not to the time since admission to the hospital.

A summary of some of the blood changes in these twenty cases is given in table 1. It will be seen that the first four cases ended fatally. Of the sixteen patients who recovered, all except the last three had a similar blood picture at the beginning of the disease, in that the monocytes were within or only slightly above the normal limits. In the last three cases, the monocytes were high at the beginning of the disease.

In the first group, the fatal cases, the leukocytes variations were similar in all four. There was a polymorphonuclear leukocytosis which in two cases reached over 24,000 per cubic millimeter during the observations. The lymphocytes were abnormally low in three of the cases and were present in about normal numbers in the fourth case. The monocytes were low throughout in all four cases and tended to fall lower toward the fatal termination. A graph is shown of the leukocyte variations in one case as an example of this group (chart 1).

In the second group, the thirteen typical cases, there was considerably more variation, but the general picture was similar in all. There was a polymorphonuclear leukocytosis. In four cases this was not high, the maximum being about 12,000 per cubic millimeter. In the

² Naegeli. Blutkrankheiten u. Blutdiagnostik.

remaining cases, a high polymorphonuclear leukocytosis, between 17,000 and 28,000 per cubic millimeter, developed. In five of these cases the number of polymorphonuclears fell sharply to about normal within twenty-four hours after the crisis, in the others, the fall to normal was more gradual.

The lymphocytes presented variations. At the beginning of the observations they were abnormally low in seven cases but were present in normal numbers in the other six. In all cases they rose later in the disease, in seven reaching high figures so that a definite postinfective lymphocytosis was present. In many cases, the observations were stopped before the lymphocyte curves were complete, but in six of the cases in which a definite lymphocytosis developed, it was found to be only transient, the lymphocytes soon falling to normal numbers.

TABLE 1—*Summary of Blood Changes in Patients with Lobar Pneumonia*

Case	Day When First Seen	Monocytes at First	Day of Peak of Monocytes	Monocytes per Cubic Millimeter at Peak	Duration of Monocytosis	Day of Crisis
1	3	Low	None			Died on 9th
2	3	Low	None			Died on 7th
3	2	Low	None			Died on 6th
4	3	Low	None			Died on 7th
5	1	Low	5	1,900	2 days	4
6	2	Low	7	2,500	6 days	4
7	2	Low	8	1,500	6 days	9
8	2	Slightly above normal	8	1,200	4 days	9
9	3	Low	9	1,900	6 days	Lysis
10	2	Low	7	1,200	2 days	4
11	3	Normal maximum	9	1,400	3 days	6
12	3	Low	6	1,100	3 days	5
13	2	Slightly above normal	5	1,400	6 days	4
14	3	Low	14	1,200	3 days	10
15	3	Low	15	900	4 days	11
16	2	Slightly above normal	10	1,300	3 days	5
17	2	Low	9	1,700	Persistent	No fall in temperature
18	2	High	8	2,600	11 days	4 (in complete)
19	1	High	4	2,100	10 days	Lysis
20	2	High	2	2,950	10 days	5

The eosinophils were absent in all cases at the beginning and appeared at varying intervals after the onset of the disease. A definite postinfective eosinophilia was observed in only two of the cases, in the others, the eosinophils remained within normal limits.

At the beginning of the observations in these thirteen typical cases, the monocytes were either within normal limits or slightly above the normal maximum. They rose in total numbers, in every case reaching a point above the normal maximum, so that a definite monocytosis was present (charts 2, 3, 4, 5 and 6). The highest point of this monocytosis varied in relation to the onset of the disease and to the occurrence of the crisis. In nine cases this peak occurred after the crisis, in two cases it occurred just before the crisis, in one case (case 9) the temperature fell by lysis, and in the last case (case 17) a fall in tempera-

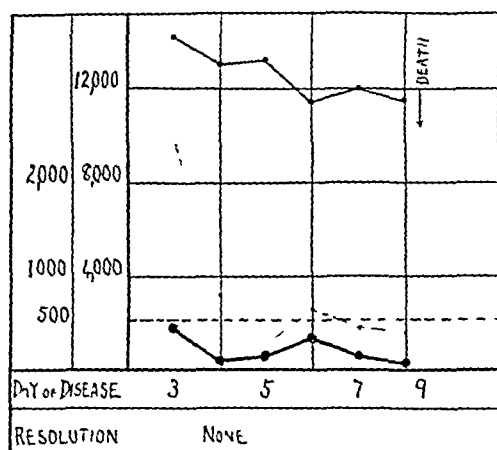


Chart 1—Graph showing leukocyte variations in case 1. In the charts the right hand column of figures represents the scale of the polymorphonuclears, and the left hand column the scale of the monocytes and lymphocytes. The continuous fine line indicates the polymorphonuclears, the continuous coarse line, the monocytes, and the fine dotted line, the lymphocytes. The horizontal dash line represents the normal maximum for monocytes.

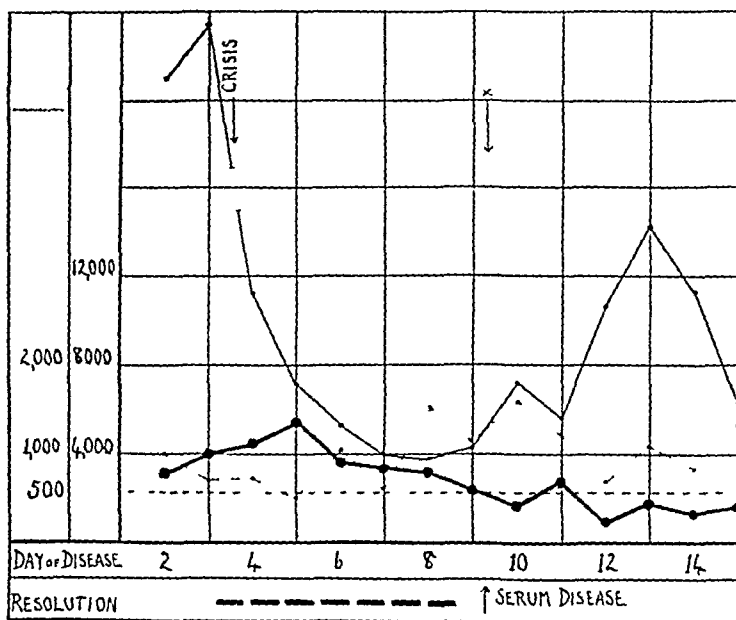


Chart 2—Leukocyte variations in case 13

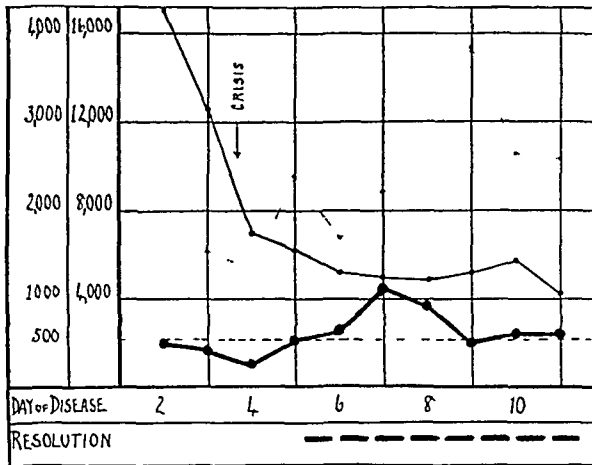


Chart 3—Leukocyte variations in case 10

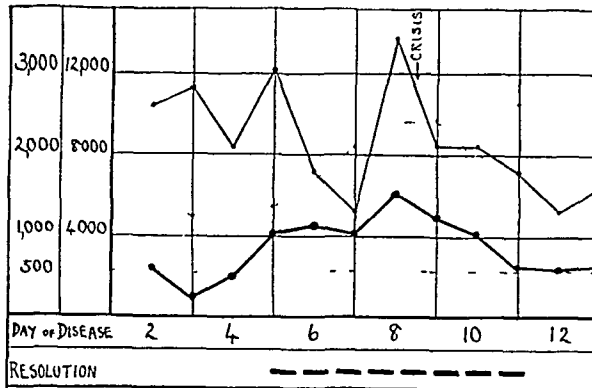


Chart 4—Leukocyte variations in case 7

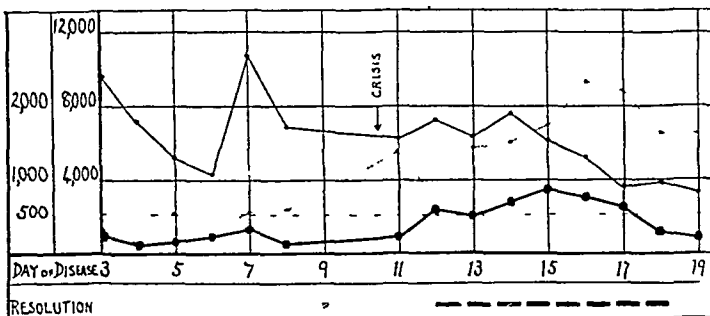


Chart 5—Leukocyte variations in case 15

ture did not occur during the observations. The duration of the monocytosis also varied. The shortest duration observed was two days, the longest was six days, except in case 17, in which the monocytosis was sustained as long as the observations were continued (chart 6). The patient in this case developed an empyema. In all

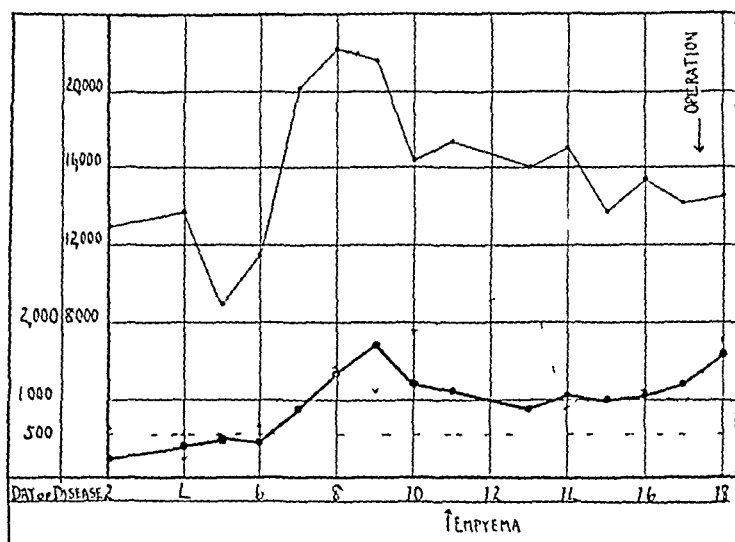


Chart 6—Leukocyte variations in case 17

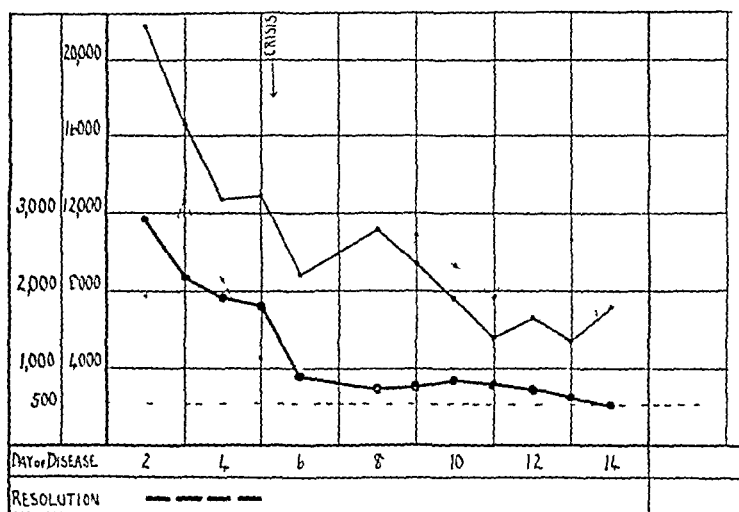


Chart 7—Leukocyte variations in case 20

cases, with the exception of case 17, the number of monocytes had fallen to within normal limits before the observations were discontinued. The main points regarding the monocytes are summarized in table 1.

It is found that the curve of the total monocytes in every case is remarkably smooth, often in spite of wide variations in the total leukocyte count (chart 2). The rises and falls occur gradually, and these curves would probably be still smoother with more accurate technic

These smooth curves indicate that it is the total count of monocytes per cubic millimeter and not the percentage which is of importance, the steady rise and fall is emphasized because it is believed to be of particular significance, especially in view of the complex nature of a clinical case in which, even under hospital conditions, it is so difficult to be sure of the presence or absence of complicating diseases

The curves showing the number of monocytes are independent of the rises and falls of the other blood cells. In most cases, the monocytosis occurs after the polymorphonuclears have resumed normal numbers, in all cases, the monocytosis precedes the rise of the lymphocytes. These facts at once suggest that the monocyte has some special function different from that of the polymorphonuclears or other blood cells.

In the last three cases in table 1 there were high monocyte counts as soon as the patients were observed, the total number of monocytes fell gradually to within normal limits before the observations were

TABLE 2—*Summary of Blood Counts Made on Patients with Lobar Pneumonia*

Case	Day When First Seen	Monocytes per Cubic Millimeter	Total Leukocytes per Cubic Millimeter	Outcome
21	2	320	11,600	Death on 3d
22	3	450	22,400	Death on 3d
23	3	70	17,600	Death on 4th
24	3	480	8,700	Recovered
25	4	80	2,600	Death on 4th
26	4	390	15,700	Death on 5th
27	4	730	12,500	Recovered
28	6	490	16,500	Death on 9th
29	6	1,400	13,400	Recovered
30	7	1,200	20,000	Death on 8th
31	7	940	11,800	Recovered
32	7	2,200	34,600	Recovered

stopped (chart 7). There was a high polymorphonuclear leukocytosis which fell gradually but irregularly to normal. The lymphocytes in two cases were abnormally low at first, and later rose, in the third the lymphocytes were not depressed in numbers at the beginning. In one case a definite but transitory lymphocytosis was observed. The eosinophils were absent at first in all cases. In two cases, a definite eosinophilia occurred later, and this was sustained for some days in one of them.

In addition to the twenty cases described in the foregoing, blood counts were performed in twelve other cases of lobar pneumonia, the results are summarized in table 2. Seven of these were counted within the first four days of the disease, and in six of them the monocytes were low, in the seventh case, they were slightly above the normal maximum. In the remaining five cases, the blood count was made on the sixth or seventh day of the disease, in four of these, a definite monocytosis was present, in the fifth case, the number of monocytes was still low.

Although one or even two or three examinations on a single patient are not of much value in this work, the results in these cases in general agree closely with those found in the more extensively studied series.

The results as far as the monocytes are concerned may be summarized as follows. In most cases of lobar pneumonia there is a characteristic reaction of the monocytes in the circulating blood. These cells, in total numbers per cubic millimeter, are within normal limits at the beginning of the disease, the numbers rise in all cases to a point definitely above the normal maximum. This monocytosis lasts for a few days. The peak of the monocytosis generally occurs after the crisis. Following the peak, the monocytes gradually fall to within normal limits.

If death occurs early in the disease, the number of monocytes is generally found to be low, when death occurs later, monocytosis may be present before death.

The significance of the monocytosis was not realized until many cases had been studied in detail, hence not all the cases were followed clinically as closely as one would have wished. It is believed, however, that there is evidence from this work that the monocytosis is intimately associated with resolution.

Reference to table 1 shows that the monocytosis in the sixteen patients who recovered occurred at three stages in the disease. In three cases there was a monocytosis as soon as the patients were seen. In the majority, the monocytosis occurred at about the end of the first week, in two cases it occurred at the end of the second week. One case from each group will be described.

In case 20 (chart 7), the patient was first seen on the second day, when there were definite signs of consolidation of the left lower lobe. On the fourth day the signs had practically disappeared, and under the fluoroscope only a haziness in the lower part of the left chest was seen without a definite shadow of consolidation. There was no doubt from the clinical signs that there had been resolution rapidly and early. The crisis occurred on the fifth day, and the further progress of the case was uneventful.

In this case a high monocytosis was present on the second day, and this gradually subsided until the number of monocytes was within normal limits (chart 7).

Case 7 is an example of the majority of cases in which the monocytosis occurred at about the end of the first week (chart 4). The patient was admitted to the hospital on the second day, he presented signs of consolidation in his right lung. The condition spread, and by the fifth day the patient had a dense shadow which appeared to involve portions of all three lobes. Evidence of resolution appeared about the same time, by the ninth day, the shadow under the fluoro-

scope was definitely less dense than before, on the eleventh day only a faint shadow was present in the right lung

The number of monocytes was within normal limits at first, there was an increase on the fifth day, and they continued to increase until the eighth day, when the peak occurred. By the eleventh day, the number was again within normal limits (chart 4)

Case 15 is an example of the cases in which monocytosis appeared at the end of the second week (chart 5). This patient was first observed on the third day, the signs in the lungs were indefinite at first, but gradually became more evident, and frank signs of consolidation appeared and spread until the whole right lung was solid. The crisis occurred on the eleventh day, at this time no signs of resolution were present, and under the fluoroscope the whole right lung was occupied by a dense shadow. Within two days of the crisis, signs of resolution were noted, percussion was not so flat, moist sounds could be heard, and bronchial breathing was not so evident. The shadow seen under the fluoroscope was definitely less dense than previously. Up to the time of the crisis, the number of monocytes had been uniformly low. At the time that signs of resolution appeared, they commenced to increase in numbers in the circulating blood, the peak of the monocytosis occurred on the fifteenth day, and at this time the fluoroscope showed a shadow at the base of the lung only, the remainder of the lung appearing to be clear. The number of monocytes had fallen to normal three days after the peak, at this time signs in the lung were scanty, and the fluoroscope showed a small shadow still present at the base. The patient made an uninterrupted recovery.

RESOLUTION

In most cases it is not possible to say just when resolution commences. It is possible, with the help of the fluoroscope, to watch a dense shadow in the lungs become much lighter or practically disappear in the course of a few days. This is the most certain evidence that resolution is taking place.

Of the patients whose cases are recorded in table 1, sixteen recovered. In six of these the resolution was watched under the fluoroscope, in all six a monocytosis appeared in the circulating blood at the time resolution was taking place, but the monocytosis did not last throughout resolution. In six other cases the monocytosis developed at the time that ordinary clinical evidence indicated that resolution was commencing, but this was not confirmed under the fluoroscope. In the other four cases the evidence was not certain, as the cases were not followed sufficiently closely. A summary of some of the clinical details of these twenty cases is given in table 3.

Signs of resolution appear most commonly at the time of, or shortly after, the crisis, and in the majority of the cases studied this was also the time at which the monocytosis appeared (table 1)

It is believed that we have here an explanation of the monocyte curves. In a typical case, a polymorphonuclear leukocytosis is present in the circulating blood during the stage of consolidation, and the monocytes remain within normal limits. The polymorphonuclears appear in the alveoli of the lung and produce the characteristic exudation. At about the same time as the resolution commences, the monocytes in the circulating blood increase in numbers to such an extent as to produce a definite monocytosis. This monocytosis does not

TABLE 3—*Summary of Clinical Data of Twenty Patients with Lobar Pneumonia*

Case	Age	Day of Disease	Type	Blood Culture	Number of Lobes	Treatment	Notes
1	34	3	1	+ after 4th day	4	Serum	Died on 9th day
2	40	3	3	+ on 5th and 7th days	2	No serum	Died on 7th day
3	37	2	1	+ on 6th day	1	No serum	Died on 6th day
4	48	3	2	— throughout	1	Serum	Died on 7th day
5	44	1	2	— throughout	1	Serum	Mild serum disease
6	42	2	4	+ on 3d day	1	1 injection of serum	Delirium tremens
7	45	2	3	Not taken	3	1 injection of 5 cc serum	Asthmatic
8	25	2	3	— throughout	2	No serum	Negio, Wassermann reaction positive
9	34	3	2	Not taken	1	No serum	Temperature fell by lysis
10	28	2	1	— throughout	1	No serum	
11	45	1	1	— throughout	2	No serum	
12	45	1	—	Not taken	1	No serum	
13	18	2	1	+ (1 colony only) on 2d day	1	Serum	Serum disease
14	31	3	3	— throughout	3	No serum	Delayed resolution
15	15	3	4	— throughout	3	No serum	Delayed resolution
16	42	2	1	+ (few colonies) on 5th day	3	No serum	Infected nasal sinus
17	21	2	1	+ on 3d day	1	1 injection of serum on 11th day	Empyema found
18	39	2	1	+ on 2d day	3	Serum	Negio
19	28	1	2	— throughout	4	No serum	Negio
20	30	2	4	— throughout	1	No serum	Rapid resolution

* All patients were men with the exception of patients 14 and 15

last throughout the stage of resolution, signs may still be present, and a light shadow under the fluoroscope may still be visible after the number of monocytes has fallen to normal.

Clinically, signs of resolution may appear at varying stages in the disease in different cases of pneumonia. There may be signs of resolution early in the disease, even before the crisis, or no sign of resolution may be present until much later than usual. Some of these atypical cases are described in this article, and the close association of the monocytosis with resolution even in these cases is pointed out. It is possible that the other cases which presented a high monocytosis in the early stages of the disease may have a similar explanation, but that the evidence clinically was not conclusive, or some undetected complicating factor may have been present.

In the four cases recorded in table 1 in which death occurred early in the disease, no clinical signs of resolution were present. The number of monocytes was persistently low in all. Unfortunately, autopsy was not performed on any of these four.

There is a small amount of pathologic evidence in support of the belief of the close association of a monocytosis with resolution. Of the thirty-two cases in the entire series, eleven ended fatally, four of these came to autopsy. In three cases (21, 23 and 25) death occurred within the first four days of the disease, the number of monocytes was low in all. Autopsy revealed massive consolidation of the lungs, which were a dirty red color and brittle on pressure on the cut surface. No sign of resolution was present. Microscopic sections of one of the lungs (case 25) showed the typical appearance in the stage of consolidation, the alveoli were filled with polymorphonuclears, debris of red blood cells and fibrin. No microscopic evidence of absorption of the exudate was present.

The patient in the fourth case (case 30) died on the eighth day. On the day before death a well marked monocytosis was present in the circulating blood. Autopsy showed that the affected lobes of the lung were resolving, on microscopic examination, the alveoli were seen to contain a few large mononuclear cells, little debris was present, and the affected portion of the lung was in an advanced stage of resolution.

It is suggested that the monocytosis in the circulating blood is an indication of an emigration of monocytes from their place of origin to the lungs to perform a function closely connected with resolution.

SUMMARY

1 A study is presented of the leukocyte variations in the circulating blood in thirty-two cases of lobar pneumonia.

2 In twenty cases, daily observations were made on the blood throughout the disease.

3 A monocytosis developed in the circulating blood of all patients except those who died early in the disease.

4 Evidence is given which shows that this monocytosis is closely associated with resolution of the affected lung.

ACTION OF DRUGS ON CARDIAC OUTPUT

IV EFFECTS OF CAMPHOR AND STRYCHNINE ON THE CARDIAC OUTPUT OF INTACT UNNARCOTIZED DOGS[†]

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AND

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Our present knowledge concerning the action of the so-called "cardiac stimulants" is incomplete. Many clinical and experimental studies have been made of their effects on blood pressure and pulse rate. The essential function of the heart, however, is to pump blood, and before evaluating any drug as to its circulatory action, information of its effects on the cardiac output is essential. Cardiometric and other observations on decerebrate or anesthetized animals with the chest opened cannot suffice for this purpose. Harrison and Leonard¹ have shown that digitalis, which has repeatedly been demonstrated to increase the output of the isolated heart, has precisely the opposite effect on the intact animal.

The rather surprising results obtained with digitalis have seemed to warrant an investigation with the newer methods of other drugs commonly used in the treatment of patients with circulatory disorders. The results of studies on caffeine are being reported in another paper. In brief, the results found were a slight diminution in minute cardiac output after doses comparable to those usually given to man for therapeutic purposes and a greater decrease with larger doses of the drug.

Camphor and strychnine are frequently employed in the treatment of patients with acute and chronic circulatory failure. A perusal of the literature suggests that their value in this respect is far from established. Thus, in regard to experiments with camphor, Sollmann³ says "These are inconstant, different investigators reporting divergent results and conclusions." Summarizing clinical reports, he adds "Camphor is used clinically as a temporary cardiac stimulant. Opinions are divided as to its usefulness. The effects, if they occur, are inconstant and

[†] From the Department of Medicine, Vanderbilt University.

1 Harrison, T R, and Leonard, B W. The Effects of Digitalis on the Cardiac Output of Dogs, *J Clin Investigation* **3** 1, 1926.

2 Pilcher, C, Wilson, C P, and Harrison, T R. The Effects of Caffeine on the Cardiac Output of Dogs, in press.

3 Sollmann, T. *Manual of Pharmacology*, Philadelphia, W B Saunders Company, 1922, p 229.

unreliable" Cushny⁴ said of camphor "its effects on the heart in therapeutically possible amounts are trifling or entirely negative" More recent pharmacologic and clinical observations support the conclusions of Sollmann and Cushny As a result of extensive investigations, Heathcoate⁵ concluded that evidence "that camphor possesses any value whatever as a cardiac or circulatory stimulant" was lacking Marvin and Soifer,⁶ after pointing out the widespread clinical use and the great faith which many physicians place in the drug, reported the results of their own careful studies Doses of from 0.2 Gm to 3 Gm failed to influence the pulse rate, respirations, vital capacity, blood pressure, electrocardiograms or general condition of normal persons or patients with cardiac failure, whereas most of the patients promptly improved when digitalis therapy was subsequently instituted The majority of favorable clinical reports concerning camphor consists of isolated cases in which the action of the drug was not well controlled

Strychnine is frequently used for its effect on the circulation, although possibly less so than a few years ago Opinions concerning its value differ Cameron⁷ found that 0.03 mg per kilogram of body weight increased the "tonicity" of the mammalian heart, slightly larger doses caused an increased cardiac output as measured by the cardiometer Edmunds⁸ observed that strychnine increased the secretion of the suprarenal glands, which augments cardiac output⁹ Cushny⁴ said that the mammalian heart is not affected by strychnine According to Sollmann,³ the "cardiac contractions are not changed" Marvin¹⁰ studied the effects of strychnine on medical students and found slowing of the heart and increased blood pressure after the administration of from $\frac{1}{40}$ to $\frac{1}{20}$ grains (0.0015 to 0.003 Gm) of the drug Cook and Briggs¹¹ observed the effect of strychnine in hypotensive conditions, and concluded that it was "by far the most satisfying cardiovascular stimulant

4 Cushny, A. R. *A Text Book of Pharmacology and Therapeutics*, Philadelphia, Lea & Febiger, 1918, p. 271

5 Heathcoate, R. St. A. Action of Camphor, Menthol and Thymol on the Circulation, *J. Pharmacol. & Exper. Therap.* **21**: 177, 1923

6 Marvin, H. M., and Soifer, J. D. The Value of Camphor-in-Oil as a Cardiac Stimulant, *J. A. M. A.* **83**: 94 (July 12) 1924

7 Cameron, J. P. Studies on Cardiac Tonicity in Mammals. *Johns Hopkins Hosp. Rep.* **16**: 549, 1911

8 Edmunds, C. W. The Importance of the Adrenal Glands in the Action of Pilocarpine, Physostigmine and Strychnine, *J. Pharmacol. & Exper. Therap.* **20**: 405, 1923

9 Odaira, T. Observations on Gaseous Metabolism and Minute Volume I. Relation to Internal Secretions, *Tohoku J. Exper. Med.* **6**: 325, 1925

10 Marvin, D. A Preliminary Report on the Effect of Strychnine and Digitalis on Man, *Arch. Int. Med.* **11**: 418 (April) 1913

11 Cook, H. W., and Briggs, J. B. Clinical Observations on Blood Pressure. *Johns Hopkins Hosp. Rep.* **11**: 451, 1903

for long continued routine administration" Cameron⁷ believed that strychnine was particularly indicated in conditions of cardiac dilatation without decompensation, and cited anemia as an example. On the other hand, Parkinson and Rowlands¹² and Newburgh¹³ reported no effect from strychnine in patients with decompensation. Lucas¹⁴ did not find any beneficial result in children with rheumatic disease of the heart. Cabot¹⁵ did not observe any benefit from strychnine in patients with various infectious diseases. Newburgh¹⁶ did not note any effect on the blood pressure in eight of seventeen patients with hypotension, and only a temporary rise in nine. He reported that strychnine sulphate in medicinal doses does not increase the output of the heart, slow the pulse or materially raise the blood pressure, and he believed that there was no logical basis for its use as a cardiovascular stimulant. Hewlett¹⁷ did not observe any effect on the size or form of the pulse wave in man, but he believed that the flow of blood through the arm was sometimes increased.

The foregoing brief review may be summarized as follows: 1. Both clinical and pharmacologic evidence indicates that camphor does not have a constant action on the heart and is not of value in the treatment of patients with circulatory disorders. 2. The evidence regarding strychnine is so conflicting that no conclusions are warranted.

METHOD

Marshall¹⁸ has recently demonstrated the feasibility of training dogs for cardiac punctures and respiratory manipulations, and has emphasized the fact that operations, narcotics and anesthetics may cause profound alterations in the cardiac output. Our experience is in accord with his. Narcotized animals were not used in these experiments, all the dogs being healthy and "trained." Operation was not performed. Occasionally the animals struggled, when this was in any sense marked, the determination was discarded.

12 Parkinson, J, and Rowlands. Strychnine in Heart Failure, *Quart J Med* **7** 42, 1913

13 Newburgh, L. H. On the Use of Strychnine in Broken Cardiac Compensation, *Am J M Sc* **149** 696, 1915

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17 Hewlett, A. W. The Pulse Flow in the Brachial Artery. V. The Influence of Certain Drugs, *Arch Int Med* **20** 1 (July) 1927

18 Marshall, E. K., Jr. Studies on the Cardiac Output of the Dog, *Am J Physiol* **77** 459, 1926

The details of our technic have been published elsewhere¹⁹ The consumption of oxygen was determined by the Benedict spirometer and Blalock mask Simultaneous samples of arterial blood and right ventricular venous blood were drawn and analyzed for their oxygen content in the Van Slyke-Neill manometric apparatus The cardiac output was calculated from the Fick formula

$$\frac{\text{cc O}_2 \text{ consumed per minute}}{\text{cc O}_2 \text{ taken up by 1 cc of blood in passing through the lungs}} = \text{No of cc of blood passing through the lungs per minute}$$

After one—in many instances two—control determinations of cardiac output, the drug was administered subcutaneously The preparations used were camphor in oil (20 per cent solution—Parke, Davis & Co) and strychnine (Parke, Davis & Co) tablets dissolved in water The doses of camphor used were 4, 8 and 15 mg per kilogram of body weight (these correspond respectively to 4, 8 and 15 grains for a man weighing 140 pounds [63.5 Kg]) The doses of strychnine used were 0.01, 0.02, 0.04, 0.08 and 0.16 mg per kilogram of body weight ($\frac{1}{100}$, $\frac{1}{50}$, $\frac{1}{25}$, $\frac{1}{12}$ and $\frac{1}{6}$ grains [0.6, 1.3, 2.5, 5.4 and 10.8 mg] for a man weighing 140 pounds [63.5 Kg])

Approximately thirty minutes after the drugs had been injected, the cardiac output was again determined In many of the experiments, a third and sometimes a fourth observation was made in order to test the duration of the effect of the drug The procedures for the individual experiments are shown in the tables

The pulse rate was counted when the samples of blood were drawn The minute ventilation was estimated from the spirometer tracing, the average respiratory depth being multiplied by the respiratory rate

In all, thirty-three experiments were carried out and 111 determinations of cardiac output were made

RESULTS

A Control Studies—In order to observe whether a subcutaneous injection per se could change the circulatory minute volume, three determinations of cardiac output were made before and after the subcutaneous administration of tap water The results are shown in table 1

In each instance the cardiac output after the injection was within 5 per cent of the value obtained before the injection The mean variation in the three experiments was —2.6 per cent in cardiac output and —4.6 per cent in the consumption of oxygen

¹⁹ Harrison, T. R., and Leonard, B. W. (footnote 1) Pilcher, C., Wilson, C. P., and Harrison, T. R. (footnote 2)

In eighteen of the thirty-three experiments with camphor and strychnine, duplicate control determinations of cardiac output were made. When these varied by more than 10 per cent, further control determinations were made, until approximately constant values for cardiac output had been obtained. In the eighteen experiments in which duplicate control studies were carried out, the maximum variations in cardiac output were +12 and -16 per cent, while the maximum variations in the consumption of oxygen were +14 and -20 per cent. The mean variations were -2.4 and -2.6 per cent for cardiac output and consumption of oxygen respectively.

Whereas these two functions remained relatively constant, the pulse rate was subject to wide variations, and consequently the output per beat was inconstant. These observations are in accord with those of

TABLE 1—Control Experiments on Cardiac Output and Consumption of Oxygen Before and After the Subcutaneous Administration of Tap Water

Animal No.	Weight Kg.	Before the Administration of 1 Cc of Tap Water Subcutaneously		Thirty Minutes After the Administration of 1 Cc of Tap Water Subcutaneously			
		Consumption of Oxygen per Min. Cc.	Cardiac Output per Min. Cc.	Consumption of Oxygen per Min. Cc.	Cardiac Output per Min. Cc.	Percentage Change in	
						Consumption of Oxygen	Cardiac Output
V _{5r}	11.1	91.6	1890	88.8	1800	-2	-5
V _{6s}	8.0	84.1	2030	84.1	1980	0	-3
V _{6t}	7.5	102.8	2820	91.6	2800	-10	-1

Marshall,¹⁸ who reported relatively little change in cardiac output and great variations in pulse rate in his group of trained dogs.

Although the cardiac output for a given animal on a given day was usually strikingly constant, wide variations were observed in some of the animals on different days, in general, the cardiac output was considerably higher than in Marshall's dogs or than in the group of animals previously studied by Harrison and Blalock.²⁰ The latter observers reported that the cardiac output per minute of normal dogs was between 100 and 210 cc per kilogram of body weight. In our experiments, one half of the control values were above the level, and the average figure was 224 cc. This may best be ascribed to anemia, which, as Blalock and Harrison²¹ have shown, causes an increase in output. All the studies were carried out on eleven dogs, and the frequent bleeding caused a diminution in hemoglobin of varying degree in all of them. As anemia

²⁰ Harrison, T. R., and Blalock, A. Cardiac Output During Anoxemia, *Am. J. Physiol.* in press.

²¹ Blalock, A., and Harrison, T. R. The Effects of Anemia and Hemorrhage on the Cardiac Output of Dogs. *Am. J. Physiol.* 80:157 (March) 1927.

increased, the cardiac output became higher. As the effects of the drugs obtained in those animals with high cardiac output were entirely similar to those found in the dogs which had lower values for this function, it is not felt that anemia affected the results in any way.

B The Effects of Camphor and Strychnine—The general condition of the animals was not affected by camphor. After the larger doses of strychnine were administered, restlessness and excitability were always observed. None of the animals died or, so far as could be observed, suffered any permanent effects from the drugs.

The pulse rate was extremely variable. In some instances a decrease was noted after the administration of the drug, in others, an increase. The average change in pulse rate after camphor (all doses) was an increase of eight beats per minute, the average change after strychnine was an increase of thirteen beats per minute. We do not attach any significance to the alterations in pulse rate, as they were inconstant and not greater than changes that may occur spontaneously.

The values for respiratory rates and minute ventilation are not included in the tables because no significant change occurred in respiratory rate or depth, and hence neither minute ventilation nor alveolar ventilation was altered. This was rather surprising, since strychnine is widely used as a respiratory stimulant. Marvin,¹⁰ however, did not observe any effect on the respiration of normal men. Lucas¹⁴ reported no effect in children. Cushny⁴ said that the respiratory rate was increased by strychnine, whereas camphor did not have any significant effect.

The consumption of oxygen was sometimes slightly increased and in other instances slightly decreased after the administration of camphor. The changes were not greater than those which occurred spontaneously in control experiments, and were usually less than 10 per cent. The average changes in consumption of oxygen were -3 , $+2$ per cent and $+2$ per cent after doses of 4, 8 and 15 mg per kilogram of body weight respectively (chart 1). An increase in the consumption of oxygen followed the administration of strychnine in practically every instance. This change was considerably greater than the spontaneous variations in control experiments. The average change with the different doses was from 11 to 34 per cent, the greatest increase occurring with doses of 0.08 mg per kilogram of body weight (chart 3). Quantitatively, the effect of strychnine on the consumption of oxygen was variable with different doses and in different dogs, qualitatively, this effect was strikingly uniform.

The arterial oxygen remained fairly constant or decreased slightly after the administration of the drugs. The venous oxygen content varied in the experiments with camphor, and the utilization of oxygen

did not show any constant changes. In the experiments with strychnine, the venous oxygen was usually diminished after the drug and the utilization increased.

The minute cardiac output was not changed in any constant direction by camphor. Increases of as much as 25 per cent and decreases as great as 30 per cent were observed, but in the majority of instances the cardiac output after camphor had been given was within 10 per cent of the output before the drug had been administered.

The effects of strychnine were considerably more uniform. Doses comparable to those used therapeutically produced an increase in cardiac

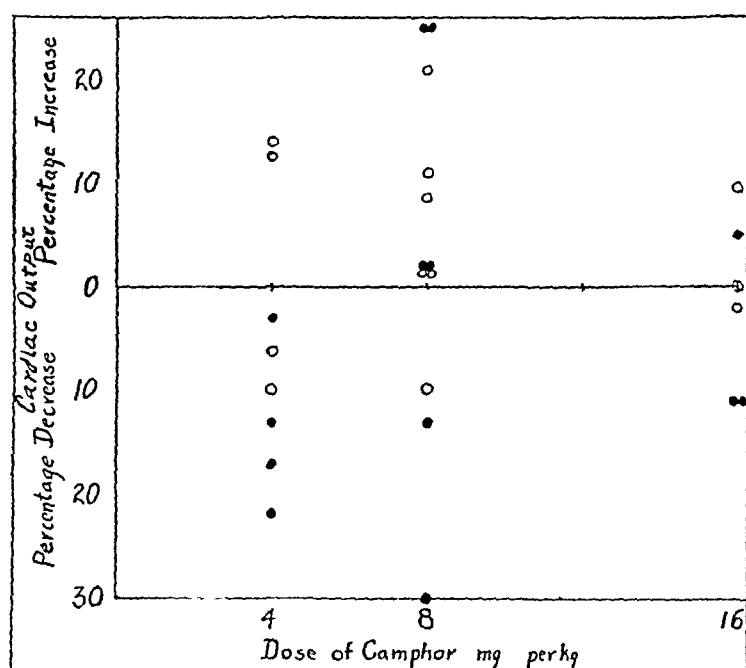


Chart 1—The majority of the values for cardiac output after the administration of camphor are within 10 per cent of the control. There is no constant tendency for the cardiac output (solid circle) to increase or decrease after the drug is given. The effects on the consumption of oxygen (hollow circle) are negligible.

output in eleven of thirteen instances. The degree of increase, however, was variable, i. e., from 1 to 56 per cent. The average increase was approximately 20 per cent, which is much greater than the limits of error of the method. Experiments showing typical effects of tap water, camphor and strychnine are plotted in chart 2.

The relationship between dosage and changes in cardiac output is depicted in charts 1 and 3. As can be seen in chart 1, the effects of camphor were variable with each dose, but no conspicuous difference is noted between the different doses, the mean values for cardiac output all falling within the assumed limits of error of the method (10 per cent).

TABLE 2—*The Effect of Camphor on Cardiac Output and Consumption of Oxygen*

Exp No	Weight of Dog	Dose of Camphor per Kilogram of Body Weight	Before Camphor		Thirty to Sixty Minutes After Camphor			Two to Four Hours After Camphor	
			Consumption of Oxygen per Minute Cc	Cardiac Output per Minute Cc	Consumption of Oxygen per Minute Cc	Cardiac Output per Minute Cc	Percentage Change in Cardiac Output	Consumption of Oxygen per Minute Cc	Cardiac Output per Minute Cc
M ₁	11.1	1	109.9	2,250	124.3	2,010	-13	111.7	2,010
M ₁₀	9.6	1	108.1	2,300	126.5	2,270	-3	120.7	2,115
M ₁₁	7.5	1	112.5	2,330	107.9	1,830	-17	106.0	2,080
M ₁₂	7.5	1	114.1	2,215	96.7	1,612	-22	91.3	1,573
M ₃	8.1	8	106.0	2,080	127.8	1,750	-25		
M ₇	7.5	8	105.9	1,400	98.3	2,110	-2		
			96.5	2,360	108.5				
M ₄	11.1	8	100.0	2,110		1,690	-30	91.2	2,430
M ₅	11.1	8	91.2	2,430	104.0	2,080	-13	94.8	2,100
M ₂	8.1	8	98.5	2,010	100	2,310	-25	93.0	1,950
M ₆	8.1	8	93.0	1,950	83.9	1,990	-2		
M ₁₂	9.0	15	92.5	2,170	86.9	2,110	-11		
			86.0	2,330					
M ₁₃	7.0	15	71.1	1,750	71.1	1,665	-11		
			71.1	1,990					
M ₁	13.6	15	111.1	2,590	122.0	2,730	-5	109.6	2,900

TABLE 3—The Effect of Strychnine on Cardiac Output and Consumption of Oxygen

Exp No	Weight of Dog	Dose of Strychnine Mg per Kilogram of Body Weight	Before Strychnine		Thirty to Forty Minutes After Strychnine			Two to Four Hours After Strychnine	
			Consumption of Oxygen per Minute Cc	Cardiac Output per Minute Cc	Consumption of Oxygen per Minute Cc	Cardiac Output per Minute Cc	Percentage Change in Cardiac Output	Consumption of Oxygen per Minute Cc	Cardiac Output per Minute Cc
S ₁₂	11 3	0 01	119 5	2,190	118 1	2,100	-17	161 1	2,610
			126 7	2,580	103 2	2,000	-4		
			97 7	2,080	81 6	2,010	-10		
S ₁₃	11 8	0 01	88 3	2,360			+13 5		
S ₁₁	7 3	0 01	69 9	2,170	89 8	2,270			2,130
			81 1	2,030			-19	85 6	
S ₁₈	8 0	0 02	81 1	1,970	90 0	2,380	+56		
			102 8	2,820					
S ₁₇	7 5	0 02	91 6	2,800	160 1	2,670	+17		
			86 5	2,390					
S ₁₀	8 0	0 02	92 0	2,310	156 6	2,660	+1		
			111 1	1,820					
S ₉	9 0	0 02	99 1	1,830	168 3	2,680	-129		
			158 0	2,830					
S ₈	11 1	0 02	132 7	2,830	117 8	1,230	0		
			82 8	1,010	128 3	1,530	+22		
S ₆	5 7	0 01	122 8	1,550	162 9	2,615	+13		
S ₅	9 1	0 01	136 5	2,036	98 0	2,110			
S ₄	11 1	0 01	91 6	1,800			+39	115 9	1,770
S ₂₀	11 1	0 01	88 8	1,880	125 3	2,610	+16 5	126 3	1,860
			93 5	1,850	115 9	1,890	+10		
S ₁₉	9 1	0 04	110 9	1,620	133 5	1,970	+3		
S ₁₀	8 6	0 08	95 6	1,790	114 1	1,340			
S ₁₁	10 0	0 05	86 5	1,350			-3		
S ₂₂	7 3	0 05	86 5	1,210	98 6	1,120			
S ₇	7 0	0 16	76 0	1,170			-2		
			70 6	1,170	107 7	1,930	-5		
M ₁₁			94 1	1,960	93 2	1,110			
S ₁₅	8 9	0 16	93 2	1,150					
S ₁₆	6 8	0 16	98 8	1,180					

With strychnine, a much more definite relationship between dosage and change in cardiac output is discernible. Subtherapeutic doses (0.01 mg per kilogram of body weight) caused slight diminution (—10 per cent) in cardiac output. Doses within the therapeutic range (from 0.02 to 0.08 mg per kilogram of body weight or from $\frac{1}{50}$ to $\frac{1}{12}$ grain [from 1.3 to 5.4 mg] for an adult weighing 140 pounds) caused an increase in cardiac output. The average values were 20, 21 and 10 per cent for 0.02, 0.04 and 0.08 mg per kilogram of body weight, respectively. It is noteworthy that the larger dose caused the least change of the three. Doses somewhat larger than those ordinarily used in thera-

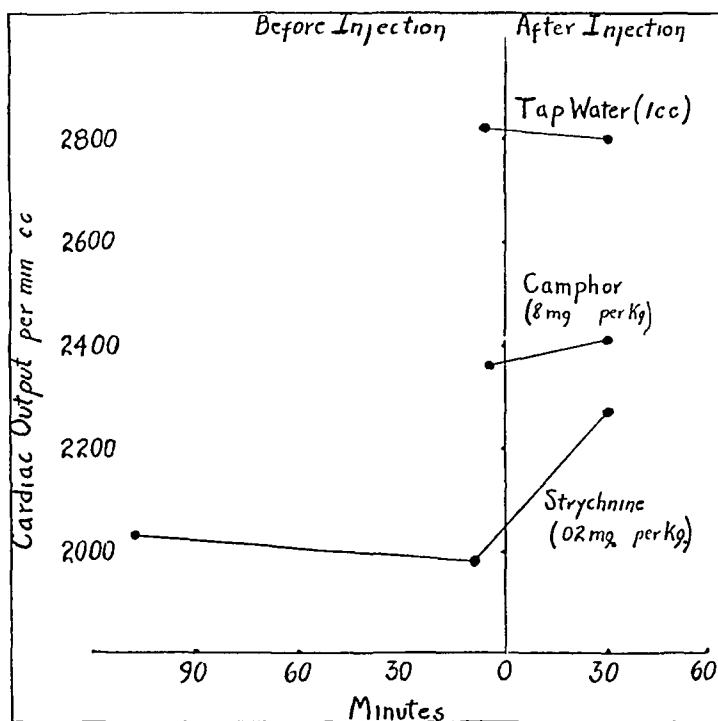


Chart 2—The effects of tap water and camphor are shown to be negligible while the cardiac output is increased from 1,980 to 2,270 cc (15 per cent) after the administration of strychnine. These single experiments represent typical results.

peutics (0.16 mg per kilogram of body weight or $\frac{1}{6}$ grain [10.8 mg] for an adult weighing 140 pounds) did not cause any significant change or cause a slight diminution in minute cardiac output. It is important to note that with any given dose the degree of increase in minute cardiac output varied greatly in different experiments.

The duration of the effects of the drugs was not carefully studied. Such changes in cardiac output as occurred after camphor usually disappeared within two hours. The effects of strychnine seemed to last for a somewhat longer time, but this point was not investigated thoroughly.

COMMENT

Camphor, strychnine and caffeine are used almost interchangeably by many physicians as "cardiac stimulants" for patients with acute circulatory failure. A comparison of the action of the drugs is, therefore, of some interest. In chart 4 the average effects of comparable

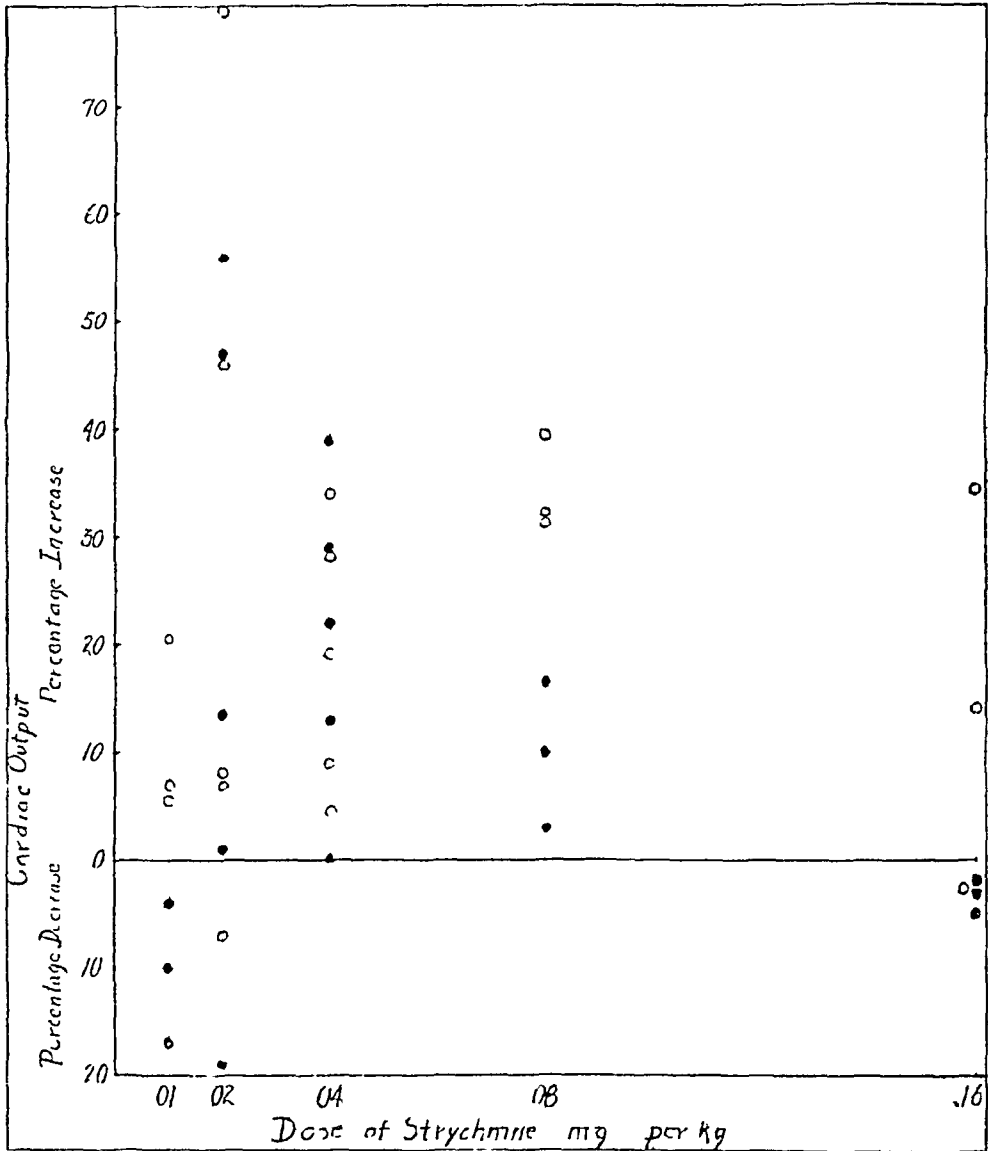


Chart 3—The effects are variable quantitatively. The largest and smallest doses, however, are followed by a slight diminution in cardiac output, whereas the output is increased after intermediate doses. The consumption of oxygen (hollow circles) is always increased to greater degree than the cardiac output (solid circles).

doses of the three drugs on the minute cardiac output of dogs are shown. The values for cardiac output after caffeine are taken from our results in another publication.²

Strychnine in "therapeutic" doses increases cardiac output, camphor does not have any constant effect, and caffeine, which in small doses

causes practically no change, produces a diminution when given in large doses. These observations suggest that it is irrational to consider any one of these drugs as a substitute for either of the others in the therapeutics of circulatory disorders.

So far as camphor is concerned, this work only adds to the rather convincing evidence already mentioned, that the drug does not have any action which indicates its value in the treatment of patients with disturbances of the cardiovascular system.

The interpretation of the results with strychnine is considerably less obvious. Since this drug has been demonstrated to increase cardiac output and consumption of oxygen, it might be argued that it consti-

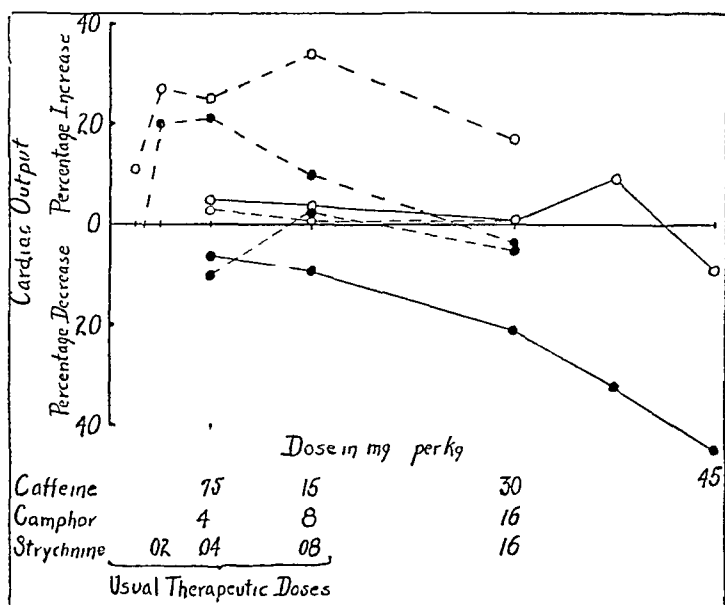


Chart 4—The average values for consumption of oxygen and cardiac output after the administration of various doses of caffeine, camphor and strychnine are plotted together so as to contrast the three drugs. Obviously, average values are of little significance when the variations in the individual experiments are marked (charts 1 and 3). However, the general tendencies of the drugs are illustrated. The consumption of oxygen (hollow circles) is not altered by caffeine (the unbroken line) and camphor (the broken line) but is definitely increased by strychnine (the dot and dash line). The cardiac output (solid circles) is practically unchanged after camphor, diminished after caffeine and usually increased after strychnine.

tutes the treatment par excellence for shock, in which both of these functions are depressed, as Aub²² and Aub and Cunningham²³ have shown.

²² Aub, J. C. Studies in Experimental Traumatic Shock. I. The Basal Metabolism, *Am J Physiol* **54** 338, 1920.

²³ Aub, J. C., and Cunningham, T. D. Studies in Experimental Traumatic Shock. II. Oxygen Content of the Blood, *Am J Physiol* **54** 468, 1920.

To this point of view there are at least two objections 1 Stychnine—in our observations at least—increases the consumption of oxygen to a greater degree than the cardiac output An increase in the consumption of oxygen means an increased demand on the circulation, and it is doubtful whether a drug which increases the demand for blood to a greater degree than it augments the flow is valuable in conditions of acute circulatory failure or shock

2 Even if the previous objections to the use of stychnine are waived, the fact remains that the quantitative effect of the drug on the cardiac output—in dogs at least—is variable “Therapeutic” doses practically always caused an increase in cardiac output, but the degree of increase was sometimes negligible and sometimes as much as 50 per cent

In chronic cardiac insufficiency or cardiac decompensation, there does not appear to be any rational basis for the use of either camphor or stychnine The latter, like digitalis, may increase tonicity, but stychnine and digitalis have opposite effects on the normal cardiac output, and the action of digitalis is much more constant

SUMMARY

The effects of camphor and of stychnine on the cardiac output of normal, unanesthetized dogs have been studied by the Fick method The doses used were comparable to those used in therapeutics

The effects of camphor were inconstant The cardiac output and consumption of oxygen were usually not significantly altered, although decreases and increases sometimes occurred

The effects of stychnine varied according to the amount of the drug administered Doses of 0.01 and 0.16 mg per kilogram of body weight did not cause any change or caused a slight diminution in cardiac output Intermediate doses—0.02, 0.04 and 0.08 mg per kilogram of body weight—caused an increased minute cardiac output The degree of increase averaged approximately 20 per cent but was variable in different experiments The consumption of oxygen was increased to a greater degree than the cardiac output

CONCLUSIONS

The evidence obtained from the study of their effects on the cardiac output of normal dogs suggests (1) that camphor has no value in the treatment of patients with circulatory disorders, and (2) that the value of stychnine in such conditions is unproved

POLLEN ALLERGY

II THE GENESIS OF SKIN HYPERSENSITIVENESS IN MAN⁴

R W LAMSON, M D

AND

HYMAN MILLER, M D

LOS ANGELES

Hereditry is apparently an important predisposition in most allergic persons, nevertheless, there are certain instances in which a carefully taker history fails to reveal the slightest evidence of any allergic manifestation in the patient's ancestors. Such instances suggest that clinical allergy, including hypersensitiveness of the skin, may develop spontaneously or may be artificially induced.

The most thorough attempts to study the latter problem have been carried out in Schloss' clinic,¹ in which it was demonstrated that normal and marantic infants absorbed unchanged egg and milk proteins. The blood of such infants may contain precipitins for the food taken, by employing the intracutaneous test, positive skin reactions were obtained in about 50 per cent of these cases. In another instance,² a boy, 10 days old, was given egg-white without manifesting symptoms. His next contact with egg was at the age of 14 months, and a definite intolerance of eggs was observed. It has been demonstrated, therefore, that precipitins and skin reactions may be induced to certain foods.

The development of a mild degree of skin sensitivity to horse serum after injection of therapeutic serums was noted by Cooke.³ The injection of such small amounts of horse serum as those used in immunization of a subject with diphtheria toxin-antitoxin is sufficient to engender skin sensitization to horse serum in about 27 per cent of the cases.⁴

From the Allergy Clinic of Dr. George Piness

1 Anderson, A. F., and Schloss, O. M. Allergy to Cow's Milk in Infants with Nutritional Disorders, *Am J Dis Child* **26** 451 (Nov.) 1923. Anderson, A. F. et al. The Intestinal Absorption of Antigenic Protein by Normal Infants, *Proc Soc Exper Biol & Med* **23** 180, 1925. Du Bois, R. et al. The Development of Cutaneous Hypersensitivity Following the Intestinal Absorption of Antigenic Protein, *Proc Soc Exper Biol & Med* **23** 176, 1925-1926.

2 Schloss, O. M. A Case of Allergy to Common Food, *Am J Dis Child* **3** 341 (June) 1912.

3 Cooke, R. A., and Vander Veer, Jr., A. Human Sensitization, *J Immunol* **1** 201 (June) 1916.

4 Hooker, S. B. Human Hypersensitiveness Induced by Very Small Amounts of Horse Serum, *J Immunol* **9** 7 (Jan.) 1924. Park, W. H. Human Hypersensitiveness to Whole Horse Serum or Serum Globulins Following Diphtheria Toxin-Antitoxin Injections—Its Importance, *J Immunol* **9** 17 (Jan.) 1924.

Thus far we have been discussing the production of hypersensitiveness of the skin in persons previously not showing clinical evidence of allergy

Stuart⁵ warns against excessive exposure of the asthmatic child to inhalent proteins to which skin tests made on him have been negative. A patient sensitive to several grasses should not be given injections⁶ with any to which he does not react. Sterling claims that if this is done, the patient will acquire sensitization for the pollens to which he was originally not sensitive. He says that this has been shown to be true by retesting the patients during the course of the desensitization treatments. The data in this article fail to support this claim.

Certain other clinical observations⁷ which, however, lack adequate laboratory control—such as skin tests—are frequently quoted as evidence that allergy may be induced by sufficient exposure to certain grains, horse dandruff and rabbit hair. In a recent summary of hypersensitiveness, Zinsser⁸ apparently considers some of these observations⁹ to be evidence that typical idiosyncrasies can be induced by previous contacts. Opposition to the views expressed in the preceding paragraphs is not entirely lacking¹⁰.

Not infrequently the first positive skin reaction to a certain food, pollen or other substance is obtained after an allergic patient has given consistently negative reactions for a month or more. This must not be considered proof that the particular sensitization has been recently acquired. It appears that this phenomenon might be explained by assuming that the sensitization had existed for some time, but that the threshold of resistance had but recently been exceeded. A similar explanation seems applicable to those cases in which the allergic symptoms were manifested only after repeated exposure to a particular exciting agent.

5 Stuart, H. C., and Farnham, M. Acquisition and Loss of Hypersensitiveness in Early Life, *Am J Dis Child* **32** 341 (Sept.) 1926.

6 Sterling, A. Pollen Protein Intoxication in Seasonal Bronchial Asthma, *New York M J* **114** 328 (Sept. 21) 1921.

7 Rackemann, F. M. Can Hypersensitiveness Be Acquired? *J A M A* **84** 489 (Feb. 14) 1925. Ratner, B. Rabbit Hair Asthma in Children, *Am J Dis Child* **24** 346 (Oct.) 1922.

8 Zinsser, H. Hypersensitiveness, *Boston M & S J* **196** 387 (March 10) 1927.

9 Rackemann (footnote 7, first reference).

10 Koessler, K. K. The Specific Treatment of Hay-Fever, Forchheimer's *Therapeutics of Internal Diseases*, New York, D. Appleton & Company **5** 671, 1914. Goodale, J. L. Pollen Therapy in Hay-Fever, *Boston M & S J* **173** 42 (July 8) 1915. Cooke, R. A. et al. The Nature of the Process and of the Mechanism of the Alleviating Effect of Specific Treatment, *J Immunol* **2** 217 (Feb.) 1917. Coca, A. F. Hypersensitiveness, Anaphylaxis and Allergy, *J Immunol* **5** 363 (July) 1920.

Numerous patients are found with a negative skin reaction (both scratch and intracutaneous) to certain pollens which according to the history are important etiologic factors. In these cases, one or more such pollens may be employed in the treatment. Frequently clinical relief is not obtained until such a pollen is used. These cases afforded us an excellent opportunity to apply a crucial test to the claims made by Steiling⁶ and others, namely, that it is possible to induce positive skin reactions by injection of pollens into an allergic person. These data obtained at the completion of the spring treatment in April and May, 1927 are presented in the tables. The methods employed in diagnosis and treatment have been previously outlined¹¹. They are essentially those in use in other Allergy Clinics and will not be repeated in detail at this time.

DISCUSSION OF TABLES

The age, sex or pollen employed has no evident effect on the results.

In table 1, twenty-three patients are considered. In all but one (case 24) the sensitizations are multiple and include sensitizations to graminæ other than those employed in treatment. Asthma is one of the diagnoses in eighteen cases, in fact, it appears alone but once. Hay-fever is present in twenty-one patients and is the only diagnosis in three of these cases. All patients considered in this table are typically allergic persons, and they show a multiplicity of sensitization, thus demonstrating a capacity for skin reactivity.

In seventeen of the thirty-three observations there has been no increase in the degree of skin reaction over that present before treatment when tested at two and four week intervals after the number of injections indicated. In twelve additional instances, in which results are available for but one of the two tests after treatment, there has been no increase in skin sensitivity. Thus, in twenty-nine of the thirty-three observations, the injection of a pollen to which the patient's reaction was formerly negative has failed to induce skin hypersensitivity. It must also be remembered that these patients have had at least one and most of them numerous seasons of natural exposure—inhalation—to these same pollens. We have previously shown¹¹ that usually injections of pollen are capable of decreasing the skin reaction in one sensitive to the pollen used.

There are four instances representing four different pollens and three patients in whom the test two weeks after treatment was considered to be more positive than before treatment, but in no instance has this been

¹¹ Lamson, R. W., Pinness, G., and Miller, H. Pollen Allergy. I. Skin Sections of Patient Before and After Treatment with Spring (Grass) Pollens, *Am. J. M. Sc.*, to be published.

shown to be the case at the last test. These three patients had not received a previous injection of the particular pollen, and the data fail to show that previous treatments make it any easier to induce skin sensitization. We believe that these four observations are well within the limit of experimental error, and that there is no evidence in support

TABLE 1—Effect of Injecting Pollens to Which Patients Were not Skin Sensitive

Patient No *	Sex	Age	Diagnoses	Pollen	Previous Treatment with Pollen Indicated	Number Treatments This Course	Skin Reactions†			Other Sensitizations
							Before Treatment	2 Weeks After Treatment	4 Weeks After Treatment	
8	F	48	A HF U	C	None	16	—	4	2	V W X
15	M	54	A HF	C	16	16	—	—	—	W X Y
21	F	6	A HF	C	None	16	—	—	—	W X Y
25	F	56	A HF	C	33	15	—	—	?	W X
39	M	38	A	C	None	15	—	2	—	V W X
61	F	65	A HF	C	None	21	—	—	?	W X
69	M	33	A HF	C	None	15	—	—	—	W X
10	F	41	HF E	C1	16	15	—	2	?	W Y
19	M	12	A HF	L1	None	15	—	—	—	W X Y
20	F	53	A HF	L1	None	17	—	4	?	W X Y
30	F	27	A HF U	L1	19	21	—	—	—	W X
80	F	30	A HF	L1	None	19	—	—	?	W X
14	F	5	A HF E	P	None	16	—	—	—	V W Y
1	F	23	A HF	P	None	20	—	2	?	W X Y
1	F	23	A HF	P4	None	20	—	—	?	W X Y
20	F	53	A HF	P4	None	17	—	—	?	W X Y
57	M	29	HF	P4	17	16	—	?	—	V W X Y
8	F	48	A HT U	A2	None	16	2	4	2	V W X
12	F	39	A HT	A3	None	15	2	2	—	V W X
25	F	56	A HT	B	None	15	2	—	?	W X
58	M	45	A HF	B	None	18	2	2	—	W X
30	F	27	A HF U	B3	None	21	2	2	—	W X
5	F	59	A HF U	C	17	15	2	—	—	W X Y
24	M	62	HF	C	16	15	2	—	—	W
29	F	33	A HF	D	None	15	2	—	?	V W X Y
44	F	47	HT	E1	None	15	2	2	—	W X
12	F	39	A HF	H	None	15	2	—	—	V W X
21	F	6	A HF	L	None	16	2	—	—	W X Y
25	F	56	A HF	L2	None	15	2	—	?	W X
67	M	11	F	L2	None	18	2	3	?	W X
5	F	59	A HF U	P	None	15	2	—	—	W X Y
21	F	6	A HF	P	None	16	2	—	—	W X Y
68	M	60	A HT	P2	None	15	2	2	?	V W X

* All skin tests unless otherwise indicated were made by the intracutaneous method. In several instances a patient was given injections with more than one pollen to which his skin reaction was negative, and his identification number may therefore appear more than once in a table. In the tables, the diagnoses in these cases are indicated by key letters which have the following significance: A indicates asthma, E, eczema, HF, hay fever, and U, urticaria. The spring pollens are indicated as follows: A indicates *Agrostis palustris* (redtop), A2, *Avena fatua* (wild oat), A3, *Amaranthus retroflexus* (rough pigweed), B, *Bromus carinatus* (California Brome-grass), B3, *Bromus rigidus* (broncho grass), C, *Cynodon dactylon* (Bermuda), C1, *Chenopodium album* (lambquarters), D, *Dactylis glomerata* (orchard grass), E1, *Elymus condensatus* (giant rye grass), F, *Festuca californica* (California fescue), F1, *Festuca elatior* (meadow fescue), F2, *Festuca rubra* (red fescue), H, *Holcus halepensis* (Johnson grass), L, *Lolium multiflorum* (Australian rye grass), L1, *Lolium perenne* (ray grass), L2, *Lolium temulentum* (darnel grass), N, *Notholcus lanatus* (velvet grass), P, *Phalaris minor* (small canary grass), P2, *Phleum pratense* (timothy), and P4, *Poa pratensis* (Kentucky blue grass). In order to demonstrate that these are truly allergic persons, we have tabulated by key letter the type of skin sensitizations present in each patient. Only strongly positive reactions have been considered. The key letters in this column have the following significance: V, epidermal structures, W, spring pollens (other than those included in the antigen), X, fall pollens, and Y, foods. As we have previously indicated, a "2" plus reaction is one that shows only a slight difference from the control and is considered a negative result.

† The reaction in patient 15 was formerly called a 2 plus (intracutaneous) and is classed as a negative one. The reaction in patient 61 was first marked a 3 plus to Bermuda, though subsequent scratch and intracutaneous tests before this course were entirely negative. Patient 69 has been tested for three years and has never been found sensitive. In patient 14 all three reactions were obtained by the scratch test. Patient 67 is suffering from eczema only, the clinical history in this case definitely indicates that pollen is the etiologic factor.

of the theory that injection of pollens to which a patient is skin negative will induce skin hypersensitiveness

In table 2 the previous reaction is indicated for each pollen mentioned. These sixteen cases furnish ample evidence that it is possible to decrease the skin reactivity as a result of specific treatment, and that after a negative reaction has been produced, subsequent injections of that pollen will in the vast majority of instances maintain the condition of "skin desensitization" rather than cause a return to the previous sensitive state.

CONCLUSIONS

1 Acquired skin sensitization to foods and horse serum seems to be an established fact. Proof that this is an example of the production

TABLE 2—*Skin Reactions to Pollens*

Patient No	Sex	Age	Diagnoses	Pollen	Previous Treatment with Pollen Indicated	Number Treatments This Course	Skin Reactions			Other Sensitizations	Previous Reaction
							Before Treatment	2 Weeks After Treatment	4 Weeks After Treatment		
28	M	38	HF E	A	21	15	—	2	—	W X Y	4 plus
17	F	24	A HF	C	35	15	—	3	—	W X Y	4 plus
40	M	36	HF	C	15	16	—	—	—	V W X	4 plus
42	F	39	A HF	C	23	15	—	—	—	V W X	3 plus
43	M	48	HF	C	46	15	—	4	3	W X	4 plus (twice)
55	F	27	HF	D	15	17	—	?	—	V W Y	4 plus
10	F	41	HF E U	F	16	15	—	—	?	W Y	4 plus
38	F	39	HF	F1	None	15	—	2	4	W	4 plus
29	F	33	A HF	F2	None	15	—	—	?	V W X Y	4 plus
12	M	52	A HF	L1	16	22	—	4	?	W X	4 plus (twice)
66*	F	30	HF I	L2	None	20	—	3	?	V W X Y	4 plus
25	F	56	A HF	N	16	15	—	—	?	W X	4 plus
76	M	31	HF	N	13	16	—	—	—	W	4 plus
24	M	62	HF	P	16	15	—	—	—	W	4 plus
57	M	29	HF	C	53	16	2	?	3	V W X Y	4 plus
25	F	56	A HF	H	None	15	2	—	?	W X	4 plus
25	F	56	A HF	P	16	15	2	—	?	W X	3 plus
55	F	27	HF	P	33	17	2	?	4	V W Y	4 plus

* Patient 66 was previously strongly positive by scratch test

of constitutional allergy is entirely lacking and is susceptible to other explanations

2 The injection of the amount of pollen commonly used for treatment is "antigenic" to the extent that it will decrease skin hypersensitivity, but it fails to induce positive skin reactions in allergic patients who previously have given negative skin reactions to the pollen. Some evidence is presented that several courses of such injections likewise fail to induce skin sensitivity.

3 It is suggested that natural exposure—inhalation of pollens—or injection of the same pollens or both are not the only factors necessary to induce skin hypersensitivity in an allergic person.

EXOPHTHALMIC GOITER AND THE INVOLUNTARY NERVOUS SYSTEM

XVI THE INFLUENCE OF SUBTOTAL THYROIDECTOMY WITH AND WITHOUT COMPOUND SOLUTION OF IODINE ON THE COURSE OF THE DISEASE

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In January, 1921, we instituted a study of fifty unselected cases of fully developed exophthalmic goiter¹. No specific therapeutic measures were employed in order to determine the natural history (spontaneous course) of the disease,² and to establish an index for the evaluation of therapeutic procedures³. From the group were excluded (a) patients who had thyroid enlargement without other manifestations of exophthalmic goiter⁴ and (b) those who, with or without thyroid enlargement, presented sympathomimetic symptoms, without significant elevation of the basal metabolism (autonomic imbalance)⁵. In the group studied, we included (1) patients with a significant elevation of metabolism on repeated readings, (2) patients whose illness was sufficiently severe to warrant residence in a hospital in which beds are at a great

From the Medical and Surgical Services of the Mount Sinai Hospital

1 Kessel, Lieb and Hyman. Studies of Graves' Syndrome and the Involuntary Nervous System, General Introduction, Am J M Sc no 3, **165** 384 (March) 1923

2 Kessel, Hyman and Lande. Studies of Exophthalmic Goiter and the Involuntary Nervous System. III. A Study of Fifty Consecutive Cases of Exophthalmic Goiter, Arch Int Med **31** 433 (March) 1923

3 Hyman and Kessel. Studies of Exophthalmic Goiter and the Involuntary Nervous System. X. The Course of the Subjective and Objective Manifestations in Fifty Unselected Patients Observed Over a Period of Two Years, in Whom no Specific Therapeutic Measures Were Instituted ("Spontaneous Course"), Arch Surg **8** 149 (Jan) 1924, Studies of Exophthalmic Goiter and the Involuntary Nervous System. XIII. The Course of the Subjective and Objective Manifestations of Exophthalmic Goiter in Fifty Unselected Patients. Observations for Five Years Without Institution of "Specific" Therapeutic Measures ("Spontaneous Course"), Arch Int Med **40** 314 (Sept) 1927

4 Kessel and Hyman. Studies of Graves' Syndrome and the Involuntary Nervous System. I. Thyroid Enlargement in Individuals without Sympathomimetic Manifestations, Am J M Sc no 3, **165** 387 (March) 1923

5 Kessel and Hyman. Studies of Graves' Syndrome and the Involuntary Nervous System. II. The Clinical Manifestations of Disturbances of the Involuntary Nervous System (Autonomic Imbalance), Am J Med Sc no 4, **165** 513 (April) 1923, Studies of Exophthalmic Goiter and the Involuntary Nervous System. XV. The Diagnosis of Exophthalmic Goiter, J A M A **88** 19, 1478 (May 7) 1927

premium, and (3) patients from the poorest sections of the city, who were subjected to constant economic strain

The present study is for the purpose of evaluating the efficacy of subtotal thyroidectomy. Since January, 1923, all patients have been advised to undergo operative treatment. The observations in the "thyroidectomy" series have been made in a manner identical with those in the "spontaneous" series. We had hoped to secure fifty consecutive patients, in order to eliminate the factor of personal choice of material. For reasons beyond our control, this was not possible.

The present report brings our records up to February, 1927, the earliest case having been under observation for four years, and the most recent for nine months, the average time of observation approximating twenty-four months.

MATERIAL STUDIED

One hundred and twenty-nine patients were observed. Of these, only 60 (47 per cent) underwent an operation. Of the 69 (53 per cent) who were not operated on, 15 died, 17 were rejected as desperate surgical risks, 28 did so well under the preliminary ante-operative medical observation that they refused surgical intervention, 3 left us and were operated on at other clinics, and the data on others are omitted, either because the patients refused to cooperate, or because their records are regarded as incomplete.

NONOPERATIVE GROUP

Fatalities—Four of the fifteen patients (group II, cases 2 and 19, group III, cases 6 and 20) who died without operative intervention, were dying of an acute thyrotoxicosis when they entered the hospital, another (group III, case 40) was observed for seven weeks, the predominating feature being a profound jaundice and cholemia resulting from a cirrhosis of the liver secondary to exophthalmic goiter, one (group III, case 70) died in a diabetic acidosis, precipitated or at least accelerated by a thyrotoxicosis, one (group II, case 18), of a carcinoma of the stomach, one (group II, case 28), of an intercurrent leukemia and one (group II, case 68), of metastases from a thyroid adenocarcinoma. In two other patients in the fatal group (group III, cases 48 and 72), operation was contraindicated by an intercurrent condition, in the one by a tuberculous kidney and in the other by an apical tuberculosis, a psychosis and a persistent thymus. Both of these patients died after six weeks in the hospital, during which time both were thyrotoxic and had marked cardiac insufficiency secondary to exophthalmic goiter. Four other patients, (group II, cases 27, 38 and 51 and group III, case 25) were not seen until the circulatory failure (due to exophthalmic goiter) was so far advanced that the circulation could not be sufficiently restored to war-

stant surgical intervention. All of these patients were over 50 years of age and all had fibrillation of the auricles, one of the men (group II, case 51) was, in addition, an alcoholic, and died suddenly as the result of a pulmonary infarct, another (group III, case 25) was a man, aged 50, whose basal metabolic rate fell from plus 33 per cent to 0 on his first admission to our hospital. Because of his excellent recovery, we did not strongly urge operative intervention. Shortly after his return home, he became worse and went to Bellevue Hospital, where three operations were performed on his thyroid gland. He returned to us, but with such severe decompensation that further operative intervention was contraindicated, and death followed shortly.

Spontaneous Remissions—Twenty-eight patients did so well that they refused operation. These patients have been carefully followed and we have complete records of eighteen. Fourteen, or 50 per cent have done splendidly. They still have a few minor symptoms, but they are economically restored, with a basal metabolic rate within normal limits. Three still have sufficiently persistent residual symptoms to interfere with their usefulness at times. One patient has done badly, he has been advised to return for operation. In this group were several who, although they were severely ill, made brilliant progress. For example, a girl (group II, case 16), aged 24, had a basal metabolic rate of plus 62 per cent which fell to plus 14 per cent, in group II, case 31, a girl, aged 21, had a basal metabolic rate which fell from plus 65 to plus 18 per cent, she did correspondingly well. Another patient (group II, case 4), has given birth to twins, and has stood the test of pregnancy splendidly, in group II, case 64 was a man with a heart block, and a substernal thyroid. His basal metabolic rate fell from plus 28 to plus 13 per cent, he resumed his work, and for over two years has been without circulatory symptoms or the manifestations of exophthalmic goiter.

Operations Elsewhere—Three patients were operated on outside of our institution (group II, cases 1 and 48, and group III, case 68), of these patients, one (group II, case 1) did poorly. When last seen, patient 68 (group III) was economically restored and symptom-free. In group II, patient 48 is somewhat improved, but at his last visit he was not economically restored or symptom-free.

Miscellaneous—Six other patients either were lost or their records were incomplete.

Operation Contraindicated—Seventeen patients either were refused operation or were told to return for operation at a later date. Of this group, thirteen were not operated on because they had an intercurrent clinical condition which required attention before the exophthalmic goiter. Thus, in group II, patient 40 had syphilis and was sent for

treatment, but later died as a result of that condition, in group II, patient 50 had a mild exophthalmic goiter and an active cholecystitis, in group II, patient 67 had a purulent ethmoiditis with optic atrophy and in group III, patient 28 had a chronic deforming arthritis with achylia, a glossitis and marked malnutrition, myocarditis and a hydrothorax. Operative intervention was out of the question, particularly in view of the fact that the exophthalmic goiter was but a small part of the clinical picture, in group III, patient 30 had multiple infections, paronychia, cystitis and pyonephrosis, and his resistance was so low that it was deemed inadvisable to attempt surgical measures, in group III, patient 33 had active tuberculosis, and was sent away for treatment. He had mild manifestations of exophthalmic goiter, despite a low-grade temperature, his highest basal metabolic rate being but plus 15 per cent. In group III, patient 43 was a young woman who was pregnant. Her basal metabolic rate fell from plus 38 to plus 20 per cent and it was decided to let her go through with the pregnancy first. After the birth of the child, her rate fell to plus 7 per cent, and she was so well that it seemed meddling to interfere with her course. In group III, patient 50 had a high grade arteriosclerosis with malnutrition, and fairly marked manifestations of exophthalmic goiter, the basal metabolic rate wavering between plus 51 and plus 37 per cent. The risk seemed much too great to warrant operation. In group III, patient 57 was a woman with mild exophthalmic goiter, who had had a nephrectomy and an oophorectomy, and who in addition had cystitis and cholelithiasis. In group III, patient 58 was a man, aged 50, with a marked diabetes mellitus and auricular fibrillation. His basal metabolic rate was plus 54 per cent. By the time that his circulation was established and his diabetes controlled, he felt well enough to refuse operation, and he made splendid progress thereafter. His last basal metabolic rate was plus 8 per cent. In group III, patient 59 was a woman, aged 59, with generalized arteriosclerosis, anginal attacks and pulmonary infarctions. In group III, patient 76 was a woman, aged 52, who had had bronchopneumonia, and who was advised to convalesce in the country. Another of this group (group II, case 62) had had a subtotal thyroidectomy three years previously, and presented a hyperplasia of the remnant. She had badly diseased tonsils, the thyroidectomy was deferred, and tonsillectomy was performed. Following this, her basal metabolic rate fell from plus 28 to plus 13 per cent, and we have not seen her since. In group III, patient 21 presented one of the most unusual pictures that we have ever seen. He was in a typical state of thyrotoxicosis with hyperpyrexia, and was rejected as a surgical risk. As we have reported elsewhere,⁶ thyroxin

6 Kessel and Hyman. Exophthalmic Goiter and the Involuntary Nervous System. XI. Causes of Death with Especial Reference to Pathogenesis and Treatment by Thyroxin of "Acute Crises," *J A M A* 84 1720 (June 6) 1925.

was given to him intravenously, and he made a complete recovery. He is now healthy and drives his truck, though auricular fibrillation persists. The two remaining patients (group II, case 26 and group III, case 45) were ordered to the country for a rest before operation, and these patients failed to return.

OPERATIVE GROUP

Sixty patients were submitted to subtotal thyroidectomy. The majority of these patients were operated on by Dr. A. V. Moschcowitz. So far as possible, all operative intervention on patients with exophthalmic goiter should be deferred during the heat of the summer months. Occasionally it was thought wise, however, to waive this objection, and in those few instances the operations were performed by Dr. A. O. Wilensky. The first thirty-one did not receive compound solution of iodine (Lugol's solution) preliminary to operation, the remaining twenty-nine were prepared with this solution. A comparison of the two groups may permit a critical analysis of subtotal thyroidectomy alone, and of the influence of iodides on the operative procedure.

Vital Statistics—There were thirty-eight women and twenty-two men in this series, the ratio approximating two women to one man. The average age of the patients was 35 years. Twenty-eight of the patients, or almost half, were over the age of 35 at the time of operation.

Immediate Postoperative Mortality—Seven patients died immediately following operation, giving an operative mortality of 11 per cent. Of these, three were from the group of thirty-one who did not receive the iodine solution, and four were in the group of twenty-nine who were prepared with this solution. A summary of these fatalities follows.

In group II, patient 21 was a woman, aged 35 years, with mild manifestations of exophthalmic goiter. Her preoperative basal metabolic rates were plus 31 and plus 30 per cent, her exophthalmos measured 21/19, and her weight was 102 pounds (46.3 Kg.). She was considered a good surgical risk. The operation lasted fifty-one minutes, and the patient was returned from the operating room in excellent condition. Shortly thereafter she developed a thyrotoxicosis with hyperpyrexia to 107 F., and died. The excised gland showed a colloid struma with areas of parenchymatous hyperplasia.

In group II, patient 46 was a woman, aged 50, who had manifestations of only a moderately severe exophthalmic goiter. Her anteoperative rates were plus 33 and plus 28 per cent, the exophthalmometer reading, 15/17, and she weighed 100 pounds (45.4 Kg.). She was also considered an excellent operative risk. The operation was performed under general anesthesia and required forty-five minutes. She had a thyrotoxic reaction with hyperpyrexia, and died within a few days. The tissue report was adenomatous goiter of the colloid type.

In group II, patient 54 was a man who was severely ill. He was 37 years of age. For five months he was carefully prepared on the medical side, his basal metabolic rate falling from plus 47 to plus 30 per cent. He was exceedingly restless and nervous, unstable and much worried concerning the outcome of the operation because of his responsibility to his family of small children. He was regarded as a poor operative risk. The operation was performed under general anesthesia and lasted sixty-one minutes. He had a severe febrile reaction, and died three days after the operation, the excised tissue showed a colloid struma with some areas of hyperplasia.

None of these three patients was prepared with compound solution of iodine. Of the four fatalities that occurred in patients who were prepared with this solution, in group III, patient 32 was a man, aged 53, who had been in the hospital twice before his last admission. On his second admission his basal metabolic rate had fallen from plus 30 to plus 16 per cent, and he had rested in the country before returning for operation. At his last admission, his basal metabolic rate was plus 63 per cent. He was prepared with the iodine solution for eleven days. The operation required twenty-seven minutes. He had an immediate reaction, the temperature rising to 105.6 F, and death occurred the next day. The excised gland showed a colloid struma.

Patient 34, group III, was a girl aged 25, who was operated on the same day as her sister (group III, patient 35), who survived and has made an excellent recovery. The two sisters were studied in the hospital for several months, during which time they did not do particularly well, and it was thought best to send them to the country for the summer. On her return, patient 34 (group III) has a basal metabolic rate of plus 43 per cent. She was prepared with compound solution of iodine. The operation lasted fifty-two minutes. She had an immediate febrile reaction to 106 F, and died the next day, the gland showing a colloid goiter with a few small areas of hyperplasia.

In group III, patient 51 was a woman, aged 36, whose basal metabolic rate fell from plus 65 to plus 43 per cent under the influence of rest and compound solution of iodine. The operation required forty-one minutes. The next day the patient had a temperature of 106 F, and she died. Section showed colloid struma with some small areas of hyperplasia.

The fourth patient who died (group III, case 67) was a woman, aged 49, whose basal metabolic rate fell from plus 42 to plus 18 per cent. She was regarded as an excellent risk, but following the operation her temperature rose to 105 F, and she died two days later, the tissue showing colloid goiter.

Three of the seven patients were regarded as good operative risks. The other four were recognized as poor risks, and three of them were

prepared over a long period of time. The report on the tissue in all seven of the patients was that it showed colloid struma, and in only one was the gland adenomatous.

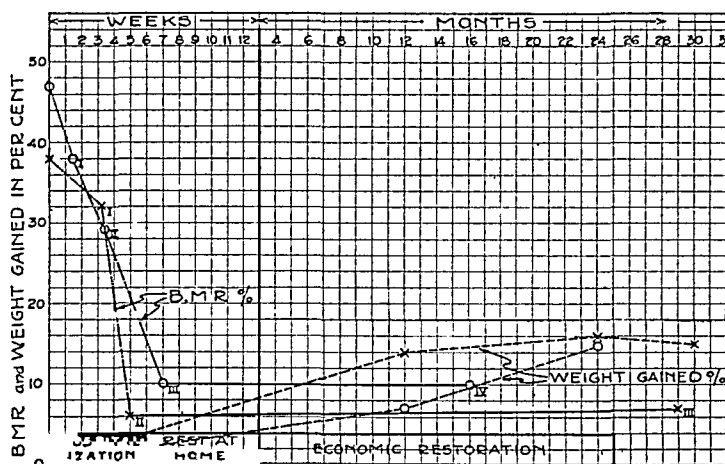
Total Mortality—Of the hundred and twenty-nine patients who formed the basis for this study, fifteen, or 12 per cent died before operation could be attempted. Seven, or 11 per cent, of the operative cases and 5 per cent of the total number of patients, died immediately following operation. Two other patients have died after their discharge from the hospital, one a syphilitic patient who was not operated on, and the other a man who had been operated on, we have been unable to learn the cause of the death of the latter. Twenty-four deaths from all causes have occurred in this group, or a gross mortality of 19 per cent.

Postoperative Reactions—Practically all of the operations were performed under general anesthesia, gas, oxygen and frequently under ether. In the group of patients who did not receive compound solution of iodine, the average time in the operating room was forty-nine minutes, and for the group that received the iodine solution, forty-one minutes. Postoperative reactions were experienced in twenty-eight of the thirty-one patients who did not receive the iodine solution, and in twenty-five of the twenty-nine patients who were prepared with the solution. The average duration of the febrile reaction in the first group was five days and in the second group, six days. Again, in the first group, fourteen patients (45 per cent) had a fastigium of 103 F or more, and in the second group, fourteen, or 49 per cent, had a temperature of over 103 F at one time or another. The longest postoperative febrile reaction was ten days. Ten patients (16 per cent), five in each group, suffered from paresis of the vocal cord, but of these, the condition was permanent in only three.

Late Effects of Operation—*Subjective Symptoms*. The vast majority of the patients experienced an immediate and striking relief from their subjective symptoms. On discharge, twenty patients (33 per cent) declared themselves to be symptom-free, and remained so for the first two years of observation. Asthenia, tremor, sweating and exophthalmos were the most marked of the persistent symptoms among those patients who were not socially or economically incapacitated. The group, including eighteen patients, or 30 per cent, have mild residual symptoms, insufficient to interfere with their livelihood. At one time or another, fifteen patients, or 25 per cent, had a marked exacerbation of symptoms sufficient to incapacitate them.

In about two thirds of the group, however, the subjective symptoms were strikingly and immediately alleviated following operation, most of these symptoms remained in abeyance during the two year period of observation in the follow-up clinic.

Exophthalmos The course of the exophthalmos was followed by frequent readings with the exophthalmometer. The average readings on admission were between 20 and 21 mm. The readings at the last observation in the follow-up clinic differed only within the limit of error of the measurement, and averaged 20.6 mm. Only four patients had a perceptible decrease in the degree of exophthalmos, and eleven had a perceptible increase. Of these eleven showing an increase in the readings, six had not received iodides, and five had been prepared for the operation with compound solution of iodine as shown in the accompanying table.



The effect of rest, iodides and subtotal thyroidectomy on the course of exophthalmic goiter. The figures to the left indicate the percentage of basal metabolic rate and weight gained. The dotted line indicated by $\times - \times I$ shows the time spent at rest in the hospital by patients who did not receive iodide, the dash and dot line indicated by $\times I - \times II$ shows the patients who did not receive iodide on whom subtotal thyroidectomy was performed, the continuous line indicated by $\times II - \times III$ shows the follow-up observations on patients who did not receive iodide, the dotted line indicated by $O - O I$ shows the time spent at rest in the hospital by patients who received iodide, the dash line indicated by $O I - O II$ shows iodide plus the time spent at rest in the hospital by patients who received iodide, the dash and dot line indicated by $O II - O III$ shows patients who received iodide on whom subtotal thyroidectomy was performed, the continuous line indicated by $O III - O IV$ shows the follow-up observations on patients who received iodide, the dash line indicated by $\times - \times$ shows percentage of weight gained by patients who did not receive iodide, and the dash line indicated by $O - O$ shows per cent in weight gained by patients who received iodide.

Weight The average weight on admission was 130 pounds (59 Kg). An average of 14 pounds (6.4 Kg), or 11 per cent, was gained in the first year. In the second year there was an average gain of 7 pounds (3.2 Kg). There was an average loss of 1½ pounds (0.7 Kg) among the patients who were under observation in the third year. The greatest gain in the first year took place in those patients who were not

prepared with the iodine solution. These patients averaged a gain of 20 pounds (9 Kg), or 14 per cent, whereas the others gained 8 pounds (3.6 Kg), or 7 per cent. In the second year, however, the average gain in weight by those who were given compound solution of iodine was 10 pounds (4.5 Kg), or 8 per cent, and only 3 pounds (1.4 Kg) for the others, as shown in the accompanying chart.

Pulse Rate We have commented on the difficulty of obtaining a basal pulse rate in patients with exophthalmic goiter. Pulse lability is universally present before operation, and persists to a lesser degree after operation. The difficulty of obtaining a basal pulse rate is great and we do not regard our observations as sufficiently accurate to warrant publication. There is, however, no doubt that the pulse rate has fallen, but a lability and a certain amount of tachycardia persist.

Cardiac Irregularities In the operative group, cardiac irregularities are extremely common in the first few days following operation. Extrasystoles, paroxysms of fibrillation and tachycardias of over 200 are often seen during the course of the postoperative reaction. Two patients (group II, case 39, and group III, case 53) developed paroxysms of auricular fibrillation and later permanent fibrillation during their convalescence. Two patients (group II, case 10, and group III, case 54), who were fibrillar before operation, continued to be so, but their cardiac reserve seemed greatly increased.

Basal Metabolic Rate Because of the influence of the iodides on the basal metabolic rate, these observations will be separated into two categories, the first dealing with the thirty-one patients who were not prepared with compound solution of iodine, and the second, with the twenty-nine who received this solution as shown in the accompanying table.

In the patients who were not given iodine solution, the average metabolic rate at the time of admission to the hospital was plus 39 per cent. At the end of a stay averaging forty-three days, the rate had fallen to plus 32 per cent, this prolonged period in the hospital before operation was due to a persistently high rate in two patients (group II, cases 11 and 54). If these two are omitted the average period is reduced to twenty-three days. The first postoperative metabolic rate was plus 6 per cent, recorded on the average thirteen days after subtotal thyroidectomy. After an average of thirty months' observation in the follow-up clinic, the last recorded rate in twenty-seven of the twenty-eight survivors was plus 7 per cent.

In addition to the last recorded rate, we have a hundred interval rate on these patients which also averaged plus 7 per cent demonstrating clearly that there was no tendency to unusual or prolonged exacerbation. Two of the patients had a rate below normal (group II, case 45, minus

Summary of the Exophthalmometer Readings*

Case No	Sex	Age	I E	L E	A B M	AL B M	AO B M	PO B M	L B M	Period Months	Section
II											
5	M	45	20/20	22/22	47		47	27	6	46	Hyperplasia
6	M	35	21/21	22/20	34		27	8	15	46	Hyperplasia
7	F	35	16/16	16/16	37		37	7	16	45	Adenoma
8	F	28	23/21		23		27	3	4	21	Hyperplasia
10	M	50	19/19	18/18	29		30	10	9	26	Adenoma
11	F	36	21/21	20/20	56		22	0	23	46	Colloid
13	F	23	21/22	20/20	32		33	0			Adenoma
14	F	23	22/23	22/22	30			0	0	42	
21	F	35	21/19		31		30				Ceased Colloid and Hyperplasia
23	M	29	32/32	28/28	22		28	8	0	7 weeks	Adenoma
25	F	44	25/25	23/23	44		34	-4	0	42	Hyperplasia
29	M	21		22/22	30		32	-6	8	39	
30	F	46	17/18	22/22	54		37	10	9	39	Hyperplasia
32	M	22	21/21		50		35	0	6	39	Colloid
37	F	31	18/20	19/20	58		43	19	12	17	Colloid and Adenoma
39	F	30	18/18	22/22	42		30	16	2	36	Adenoma
41	F	25	19/19	20/20	35		16	6	12	16	Adenoma and Colloid
43	F	47	23/23	26/24	18		22	22	5	35	Hyperplasia and Adenoma
											Carcinoma
44	F	37	16/16	17/17	57			17	4	24	Adenoma
45	F	30	18/17	19/19	51		28	3	0	33	
46	F	50	15/17		33		28				Ceased Adenoma
47	F	47	22/22	23/23	26		25	0	18	33	Adenoma
49	M	43	19/19		50		43	4	-6	11	Adenoma
54	M	37	24/24		47		30				Ceased Colloid
55	F	32	25/25	25/25	18			0	28	29	Colloid and Adenoma
57	M	41		22/22	42				0	6	Adenoma
63	F	21	14/15		32		37	-14			Adenoma
59	F	25	21/21	25/23	-9		-4	9	9	24	Carcinoma
III											
56	F	25	16/16	16/16	45		38	0	4	10	Colloid
64	M	20	21/21	21/21	31		36	8	0	13	Colloid and Hyperplasia
65	M	57			21			40	0	9	Colloid
1	F	16	23/24		18	17	20	-5			Adenoma
2	F	24	25/25	24/26	32	38	24	0	9	25	Adenoma
3	M	58	19/18	19/19	65	65	32	12	30	26	Adenoma
4	M	30	15/16		40	26	6	12			Adenoma
5	F	39	15/14		30	30	6	-4	8	23	Adenoma
12	F	22	17/17		33	18	13	5			Colloid and Adenoma
13	F	20	22/20	22/22	12	14	10	-4	14	21	Colloid
14	F	48			14	15	10	-10	-5	24	Hyperplasia
19	M	25	17/14		52		56	25			Colloid
22	F	37	17/17	21/21	56	56	45		32	22	Colloid
23	F	26	18/18		12	25	0	10			Hyperplasia
32	M	53	17/17		63						Ceased Colloid
34	F	25	26/26		43		48				Ceased Colloid
35	F	18	21/21	17/17	50		40	37	0	9	Colloid
41	F	48	16/16	17/17	50		36	11	0	17	Colloid and Adenoma
42	F	3	17/17	21/21	34		40	9	12	17	Colloid and Adenoma
46	M	47	20/20	25/25	37		46	13	9	14	Colloid
38	F	38	18/18		58		30	8			Colloid and Hyperplasia
47	F	20			74		26	26	46	2	Hyperplasia and Colloid
49	F	27	19/20	20/20	70		38	30	-3	16	Adenoma
III											
51	F	36	20/20		65		43				Ceased Colloid
53	M	38	23/25	24/25	90		37	9	9	13	Colloid
54	M	41	22/22	23/23	55		25	12	4	10	Colloid
55	M	30	21/22	24/24	44		48	20	13	14	Colloid
61	M	47	23/24	24/26	76		30	18	-6	13	Hyperplasia
67	F	49	25/25		42		18				Ceased Colloid
69	F	25		22/22	57	35	35	6	14	11	Colloid
77	M	33	20/18	20/20	42	42	14	5	17	3	Hyperplasia
71	M	43	22/22		56	36	39		0	8	Hyperplasia

* I indicates first reading, L last reading B M, on admission, B M before compound solution of iodine B M, after Lugol's solution and before operation, B M, after operation and B M, last observation. The span is the total observation from the time of admission and usually corresponds with the date of the last basal metabolic rate. The last column on the right shows the tissue report.

16 per cent, and group II, case 63, minus 14 per cent) without clinical evidence of myxedema. Four patients had a reading of higher than plus 18 per cent at the last reading.

In the series that were given iodine solution, the average rate on admission was plus 47 per cent. For an average of ten days the patients rested in bed, during which time there was a fall to plus 38 per cent. For the next two weeks compound solution of iodine, 10 minims (0.6 cc) three times a day, was administered, and there was a fall in the rate to an average of plus 29 per cent. Following operation the average basal metabolic rate was plus 10 per cent, and the last rate, taken on an average of sixteen months after admission, was also plus 10 per cent. Three patients still have a rate higher than plus 18 per cent, the highest being plus 46 per cent in a woman who was having an exacerbation of symptoms. Six patients had minus readings, of whom only one (group III, case 14) presents the clinical picture of myxedema.

All of the basal metabolic rates were estimated for us by Dr. Herman Lande and Miss A. K. Steiner. Without their assistance, we should not have been able to compile so completely these figures, which we regard as the most important of our objective observations.

Social and Economic Restitution. The period of hospitalization averaged six and a half weeks, and the period of economic incapacitation approximated from three to four months. Following this time, with the exceptions to be noted below, social and economic restitution occurred. This, as we have previously noted, is the most important desideratum from the standpoint of the individual patient. The patients who received compound solution of iodine were institutionalized for exactly the same length of time as the others, and they were incapacitated for an almost identical period. Of the fifty-three patients who survived operation, thirty-eight (63 per cent) have made a practically complete recovery and have maintained their improvement over a period averaging two years. Fifteen patients (25 per cent) have suffered at some time from their original symptoms to a sufficient degree to interfere with their social and economic restitution. In the series of patients who were given iodine solution, one patient (group III, patient 3) still suffers from symptoms mostly attributable to a duodenal ulcer, one (group III, case 12) has had a persistence of her symptoms sufficient to cause incapacitation, one (group III, case 22) has cardiac insufficiency, and one (group III, case 41) has a psychosis. In group III, patients 42, 49 and 55 have had partial and temporary interference with their livelihood, due to exacerbation of symptoms. In those patients who did not receive iodine solution, one (group II, case 5) had a persistent tremor that interfered with manual work, one (group II, case 10) had a persistence of the auricular fibrillation which prevented

him from working for eight months, one (group II, case 11) had a persistence of symptoms and a psychic instability that caused intermittent periods of incapacitation, one (group II, case 30), though there was a persistence of symptoms for about a year, is now doing fairly well, and another (group II, case 39) had a complete recurrence, after two years of relief, with hyperplasia of the remnant of the thyroid. The patient was readmitted to the hospital, but refused to submit to further operation, and is economically incapacitated. In group II, patient 45 had persistent symptoms for about a year, and is now doing well, patient 55 has had persistent and incapacitating symptoms for thirty months, up to the present time. After four years of convalescence, patient 6 (group II) developed a temporary exacerbation, which has now quieted down. In group II, patient 23 died two years after operation.

In the patients who survived the operation, the majority were socially and economically restored within five or six months following admission to the hospital, and they have maintained this improvement after their return to the wear and tear of metropolitan life.

Histology Because of the effect of compound solution of iodine on the histology of the thyroid, we shall speak again of the two classifications of patients, that is, those who received iodine solution, and those who did not.

Twelve of the patients who were not given iodine solution, had thyroid adenoma characterized by varying degrees of hyperplasia. The age of these patients averaged 36 years, the basal metabolic rate was plus 36 per cent, and there were eight women and four men in this subgroup. Seven of the twelve presented clear-cut exophthalmos, the reading being over 18/18. Except that the average exophthalmometer reading was slightly less than that for the remainder of the group, all of the other clinical features were identical with those of the non-adenomatous group, and these figures furnish no reason for believing that there is a clinical pathognomic picture of thyroid adenoma. Nine patients presented diffuse hyperplasia, and nine diffuse colloid goiters. One patient presented the histologic picture of carcinoma, but she had none of the clinical features of malignancy and no evidence of recurrence or metastases. This serves again to emphasize the hazard of making the diagnosis of malignancy from the histologic appearance of the thyroid gland. Of the three patients who died, two had simple colloid goiters and one an adenomatous gland with colloid. In none of the three fatal cases was the so-called characteristic hyperplasia the predominating histologic picture.

Eight of the patients who received iodine solution had adenomas of the colloid type. The average age of these patients was 34, the basal metabolic rate was plus 45 per cent, and the exophthalmos measured the same as that of those in the nonadenomatous group. In their response

to iodine solution, four of the eight patients had a striking fall in the rate, this was as satisfactory as the response in the nonadenomatous group. Neither in their clinical appearance nor in their response to the iodides did the patients with adenoma differ from the whole group. None of them suffered an exacerbation of symptoms on the exhibition of the iodides. Seventeen patients had a simple colloid gland, and all four of the fatalities occurred in this group. Despite the administration of iodine solution, four patients presented a gland in which there was characteristic hyperplasia, and these patients did at least as well as the average.

A recapitulation of these observations indicates that in twenty of the sixty operative cases the patients had adenomas, and that these patients did not differ from those in the nonadenomatous group either clinically or in their response to the iodides. Of the seven patients who died, one had an adenoma and six had a simple colloid goiter. None of the patients died who presented the histologic picture of hyperplasia.

The Effect of Compound Solution of Iodine Following a period of ten days of hospitalization, compound solution of iodine in doses of 10 minims (0.6 cc), three times a day, was administered to the patient in the last twenty-nine reported operative cases. In fourteen there was a perceptible and striking therapeutic result. Four of the eight patients with adenoma showed marked decreases in the metabolic rate, in one, the rate fell from plus 65 to plus 32 per cent, in another, from plus 26 to plus 6 per cent, in a third, from plus 30 to plus 6 per cent, and in a fourth from plus 70 to plus 38 per cent.

In the twenty-one patients who did not have adenomas, there was a strikingly good result in ten. Some of the changes were from plus 25 to plus 6 per cent, from plus 74 to plus 26 per cent, from plus 65 to plus 43 per cent, from plus 90 to plus 37 per cent, from plus 55 to plus 25 per cent, from plus 76 to plus 30 per cent, from plus 42 to plus 18 per cent, from plus 42 to plus 14 per cent and from plus 57 to plus 5 per cent. The remaining patients showed practically no effect from the administration of iodine solution. Two patients had a slight exacerbation of symptoms while the solution was being administered. Neither of these patients had adenoma. Both stood the operation well, and they have done well since. Whether the exacerbation was the result of the iodides or not, is debatable.

SUMMARY

- 1 One hundred and twenty-nine patients have been studied in order to determine the effect of subtotal thyroidectomy on the course of exophthalmic goiter.

- 2 Sixty-nine patients were not submitted to operation because of factors beyond our control.

3 Sixty patients had subtotal thyroidectomy, thirty-one of whom did not receive preliminary preparation with iodide

4 A comparison of the two groups affords an evaluation of the efficacy of the iodides

5 The immediate postoperative mortality in the group was 11 per cent The total mortality in the entire group was 19 per cent The effect of the operation on the subjective and objective observations and on the social and economic restitution of the patients is discussed

6 The relationship between the histologic appearance of the gland and the clinical observations and the effect of the iodides is discussed

7 The purpose of this paper is to furnish the data by which a comparison can be made between the course of the disease when observed without the institution of specific therapeutic measures and when subtotal thyroidectomy and iodides are used ⁷

7 Hyman and Kessel Studies of Exophthalmic Goiter and the Involuntary Nervous System XVII The Management of Patients Suffering from Exophthalmic Goiter, to be published

WATER METABOLISM

V EFFECT OF VARYING DEGREES OF HYDRATION ON SUGAR METABOLISM ⁴

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AND

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In a previous communication,¹ it was shown that the relative hydration of the organism had a profound effect on the sugar metabolism. If one-half unit of insulin per kilogram of body weight was injected into dogs in varying degrees of dehydration, the hypoglycemic effect was not only intensified, but it was also materially prolonged. This paper consists of further studies on the subject.

The experiments were repeated on diabetic dogs. We used not only dogs with complete diabetes, but also a dog in which the diabetes was not complete, so that he was able to remain in fairly good health for several months without the use of insulin, except as it was required for the experiments. The blood sugar estimations were made by the micro method of Folin-Wu.²

Chart 1 is a control showing the normal curve of a diabetic animal. The nocturnal hypoglycemia which has already been studied and reported³ in clinical cases of diabetes is clear. Chart 2 shows the effect of the injection of one unit of insulin per kilogram of weight in the morning, if the dog is hydrated by the administration of large amounts of fluid. The animal shown in this curve received (weight 6 Kg) 450 cc of 6 per cent sodium chloride solution subcutaneously and 80 cc intravenously, and was made to drink 500 cc of water. It is evident that if insulin has any effect in this case, it is slight. The curve is essentially like that of the control without insulin. In fact, the return to the hypoglycemic condition is slightly more rapid than in the dog who did not receive insulin. In most diabetic animals there is a condition of anhydremia due to the diureses, but in this case the dog chosen had a mild diabetes, was not very sick and not dehydrated.

The effect of dehydration on the insulin curve of a diabetic animal is even more marked. Chart 3 illustrates three such experiments. In

* From the Department of Surgery, University of Illinois College of Medicine.

1 Andrews, E. Water Metabolism, IV, Arch Int Med **38** 136 (July) 1926.

2 Byrd, B. T. Micro-Folin-Wu Method of Quantitative Blood Sugar Estimation, using One-tenth of One Centimeter of Blood, J Lab & Clin Med **11** 67 (Oct) 1925.

3 Jonas, L. All Day Blood Sugar Curves, Arch Int Med **35** 289 (March) 1925.

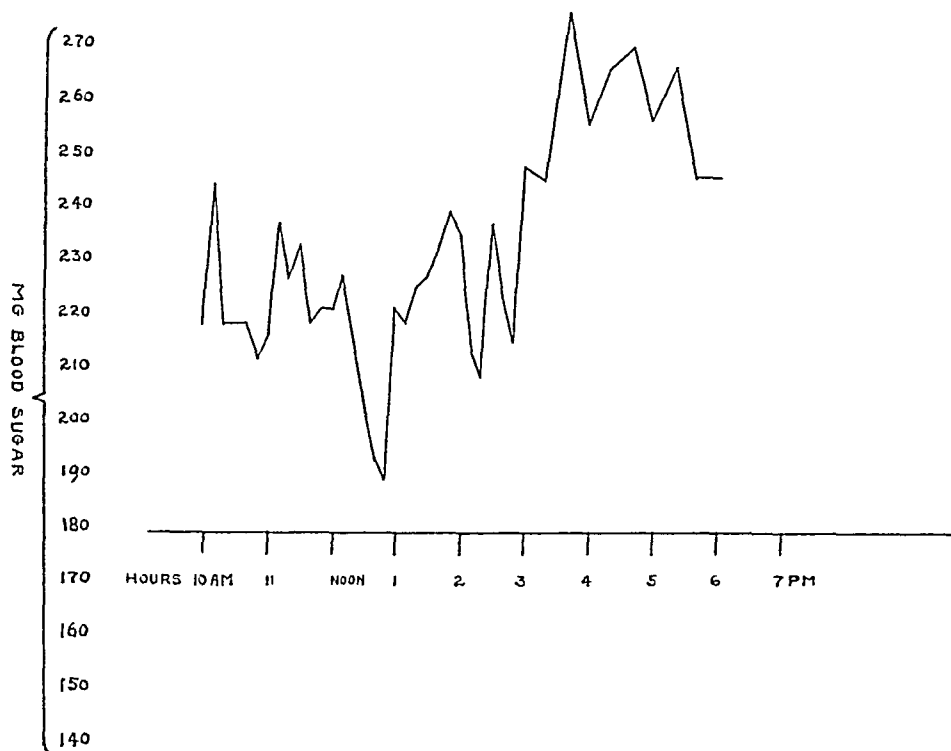


Chart 1—Control curve of a depancreatized dog (control)

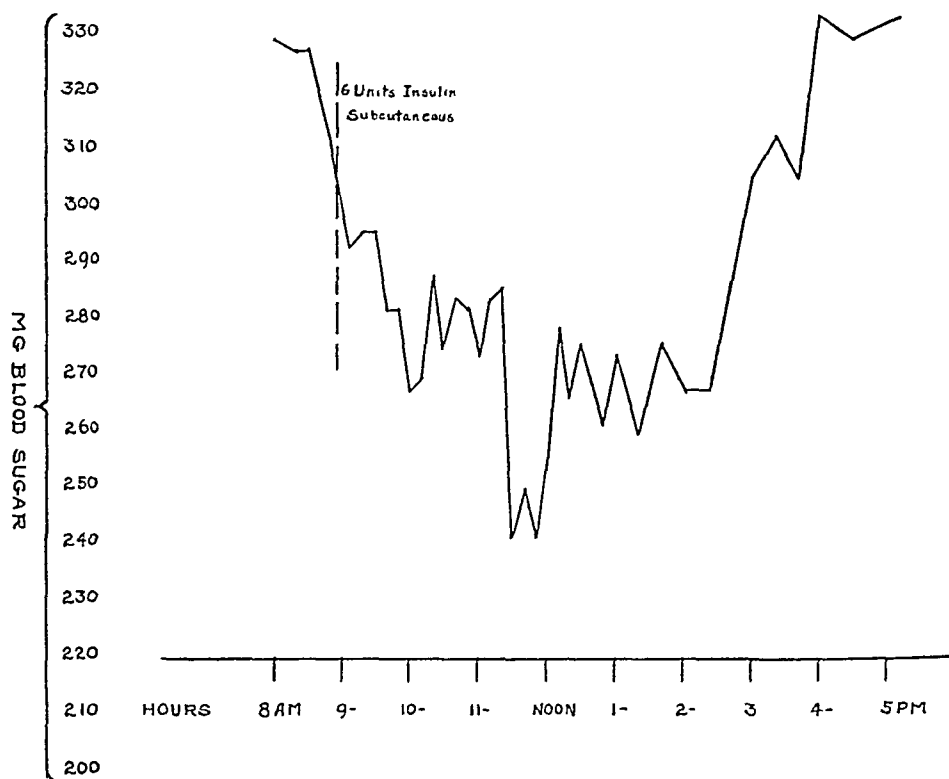


Chart 2—Curve of a depancreatized dog that weighed 6 Kg. The animal was hydrated by the administration of 450 cc of 0.6 per cent solution of sodium chloride, subcutaneously and 80 cc intravenously and 500 cc of water by mouth. One unit of insulin per kilogram of body weight was given subcutaneously.

each case the hypoglycemic effect of the administration of one unit of insulin per kilogram of body weight is tremendously exaggerated. After the period when there is generally a sharp upward bend in the control curves, the fall in blood sugar continues steadily and rapidly and lasts until the late evening at least. In curve A it is striking to note the effect of a small drink of water in bringing about a rise in the blood sugar.

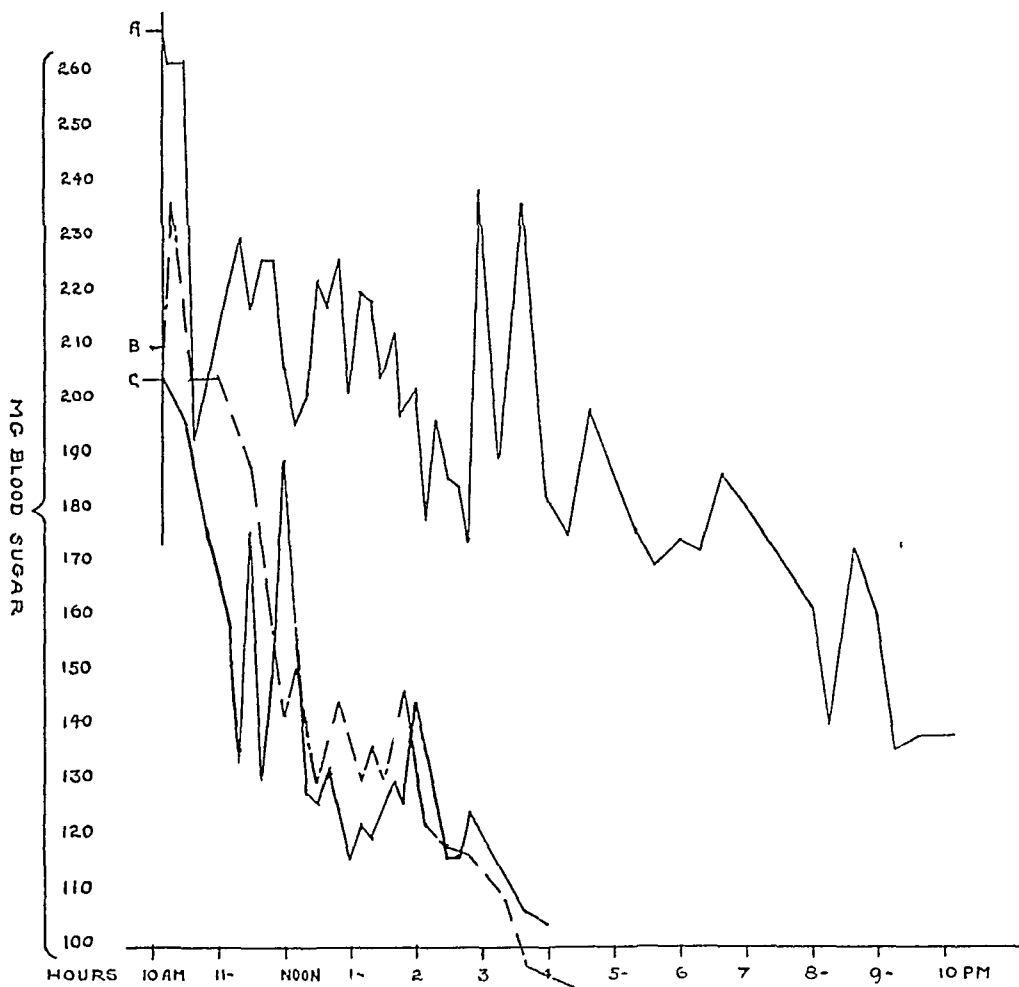


Chart 3—Curve of dehydrated dogs given 1 unit of insulin per kilogram of body weight. *A* represents the curve of a depancreatized dog that drank little water, *B*, the curve of a dog that did not drink water for eighteen hours before the experiment, the animal urinated during the eighteen hours, 225 cc at each time, *C* is the curve of the third dog. Note the rise of the curve after the dog drank a little water.

In a former paper by one of us (E. A.), it was suggested that other factors than the insulin might be the cause of these phenomena, but the following experiment (chart 4) shows clearly that the explanation must be sought in the physiologic mechanism of the action of insulin and not in any other factors. Attempts were made to modify the daily curve of the blood sugar by varying the hydration of the tissues in

diabetic dogs Dogs that had complete diabetes were used They were dehydrated by diuresis, and this dehydration was increased by deprivation of water for twenty-four hours Other dogs were allowed to drink all the water they wanted, and in addition, were given large amounts of physiologic sodium chloride solution hypodermically The resultant curves were essentially the same It is clear, therefore, that variations in the sugar curves occur only after injections of insulin

Normal animals also were tested, and variations were not found in the daily blood sugar curve (chart 5) These results show that the variations in the action of insulin are not due to any change in the production of insulin by the pancreas in the varying degrees of hydration

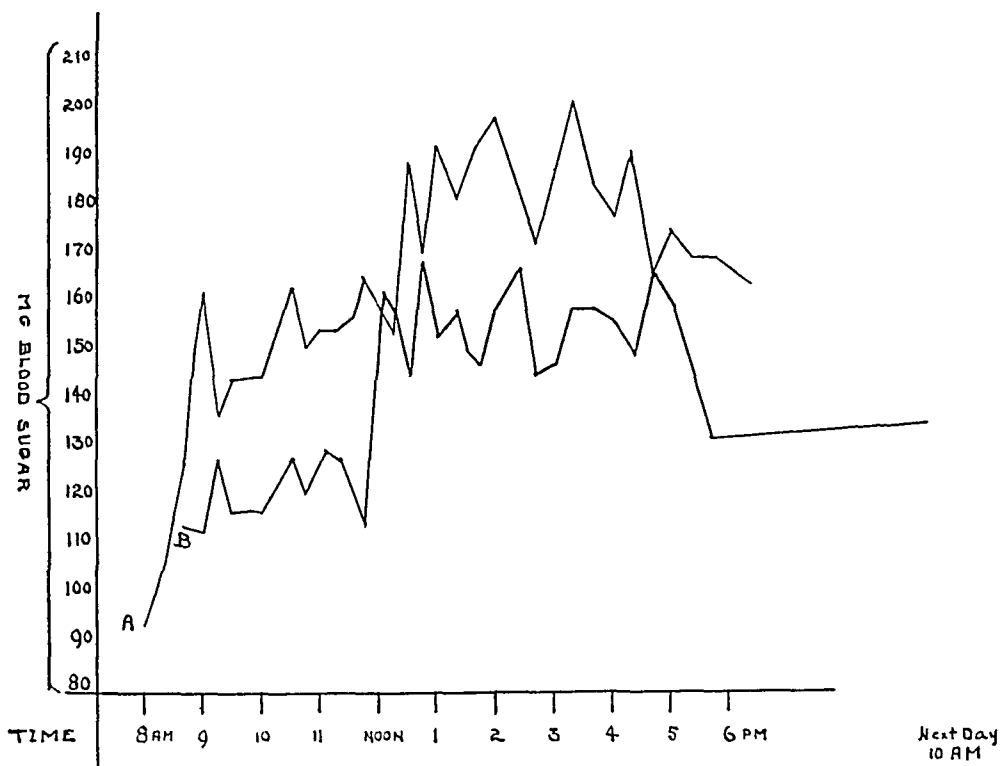


Chart 4—Curves of the depancreatized dogs that were not given insulin *A* represents the curve of the dog (control) that was not given food or water for twenty-four hours, *B*, the curve of the dog (control) that was hydrated by the administration of 70 cc of water by mouth and 430 cc of 0.6 per cent sodium chloride solution subcutaneously

COMMENT

The literature on conditions which influence the action of insulin is not large. Cajori⁴ and others report a series of investigations in which by relatively slight changes in the blood supply of limbs of patients, the

4 Cajori, F. A., Crouter, C. S., and Pemberton, R. Effect of Circulation Changes on Carbohydrates Utilization, *J. Biol. Chem.* **66** (Nov.) 1926

carbohydrate utilization was markedly affected. Bartlett⁵ investigated the average fall in blood sugar after the administration of 10 units of insulin to human beings. In normal persons the average fall was 28 points, in subjects who were emaciated and underweight it was 59 points and in diabetic persons, 70 points. Kahn⁶ has made similar observations. The results of these experiments closely parallel our observations. In 1922, Joslin⁷ noted that patients weakened by diarrhea are subject to hypoglycemic reaction. In a study of the treatment of marantic infants with insulin, Tisdall and others⁸ report that in such subjects the effect on the blood sugar was extremely variable, and often a fall in the blood sugar did not occur. The important studies of Schiff and Choremis⁹ also are of interest in this connection. They found that

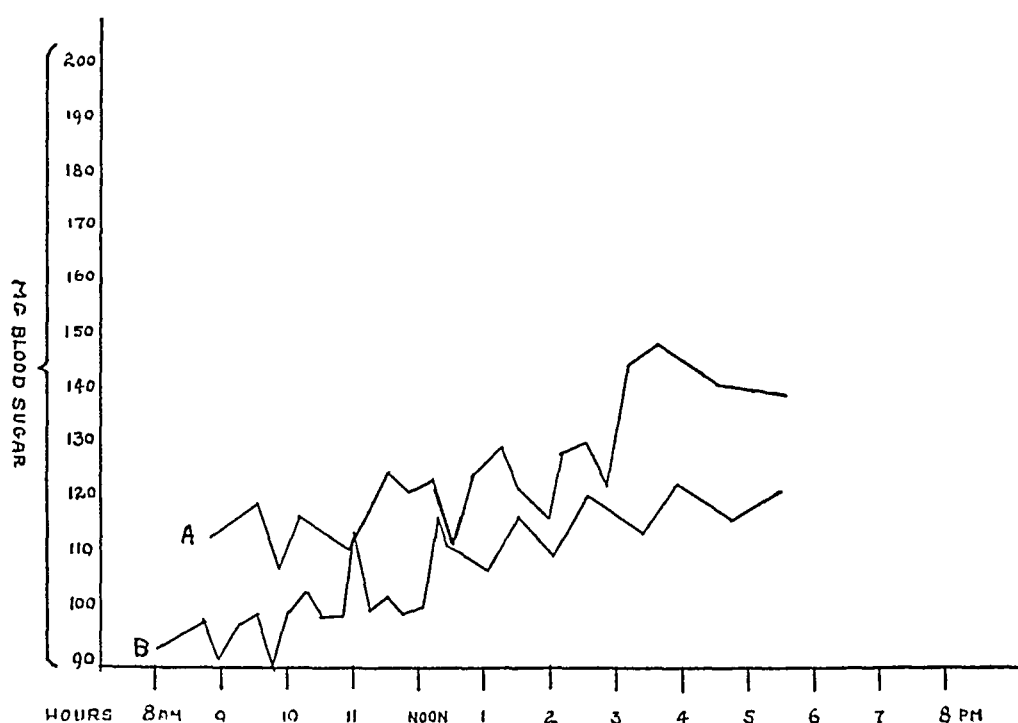


Chart 5—Curves of normal dogs. *A* represents the curve of a normal dog (control) that did not receive water for thirty-six hours nor food for eighteen hours, *B*, the curve of a dog (control) that was hydrated by the administration of 200 cc of 0.6 per cent sodium chloride solution subcutaneously, 80 cc intravenously and 140 cc of water by the mouth.

5 Bartlett, W. M. Effect of Hypodermic Injection of Insulin on Fasting Blood Sugar of Normal and Diabetic Subjects in Relation to Percentage of Normal Weight, *J. Lab. & Clin. Med.* **12** 115 (Nov.) 1926.

6 Kahn, S. H. Reduction of Blood Sugar by Means of Insulin, *Boston M. & S. J.* **191** 161 (July 24) 1924.

7 Joslin, Gray, and Root. *J. Metab. Research*, **2** 161, 1922.

8 Tisdall, F. C., Drake, T. G., and Brown, A. Carbohydrate Metabolism of the Marantic Infant, *Am. J. Dis. Child.* **30** 829 (Dec.) 1925.

9 Schiff, E., and Choremis, C. Insulin and Experimental Alkalosis, *Deutsch. Med. Wchnschr.* **52** 1732 (Oct. 8,) 1926.

the administration of sodium bicarbonate in doses large enough to produce a definite alkalosis caused a definite inhibition in the action of insulin. They also showed¹⁰ that the hypoglycemia of fasting was prevented by the administration of large amounts of fluid. These phenomena are interesting in view of the enormous amount of recent literature on fevers in the new-born and on dehydration fevers in children, as hypoglycemia has been reported in both conditions. The assumption by these authors that alkalosis is a factor in such conditions, however, does not rest on a firm basis and is contrary to the experience of most clinicians. In fact, Collip¹¹ has shown that hypoglycemia caused by insulin is accompanied by marked acidosis and even by ketonuria. Roche and Roche¹² report marked changes in the amount of glycolysis due to variations of the p_H of the blood, and conclude that the glycolytic enzyme is sensitive to such changes, but MacLeod¹³ has made elaborate investigations which render it extremely improbable that insulin is concerned in glycolysis.

The more recent work of Lawrence¹⁴ supports this view. He has demonstrated that injection of standard doses of insulin into diabetic patients causes different reactions according to the activity of the patient. If he is actively exercising, the hypoglycemic effect will be far more marked than if he is at rest. Lawrence's observation that the action of insulin is greatest in debilitated patients accords with our observations and those of Bartlett⁵. He thinks that it is greatest when the stores of glycogen in the liver are exhausted. These facts can fit in only with the assumption that the action of insulin is that of building up, not of burning, carbohydrate. If insulin is to be considered as a glycogen maker, as is now generally believed, the mobilization of sugar for consumption is seen to be the important factor in the regulation of the blood level. Lawrence's theory that there is direct antagonism of the secretions of the suprarenal and the thyroid glands to the action of insulin, however, cannot stand up so well against many of the data given in the literature.

10 Schiff, E., and Choremis, C. Exsiccation and Carbohydrate Metabolism, *Jahrb f Kinderh* **114** 42 (Sept) 1926

11 Collip, J. B. Occurrence of Ketone Bodies in Urine of Normal Rabbits in a Condition of Hypoglycemia Following the Administration of Insulin, *J Biol Chem* **55** 38, 1923

12 Roche, A., and Roche, J. P_H Concentration and Glycolysis, *Hospitalstid*, **69** 985 (Oct 14) 1926, abstr *J A M A*

13 Eadie, G. S., MacLeod, J. J. R., and Noble, E. C. Insulin and Glycolysis, *Am J Physiol* **65** 462 (Aug) 1923. Hepburn, J., Latchford, H. K., McCormick, N. S., and MacLeod, J. J. R. Sugar of Arterial and Venous Blood During Action of Insulin, *Am J Physiol* **69** 555, 1924

14 Lawrence, R. D. Action of Insulin in Glycogen Formation, *Quart J Med* **20** 69 (Oct) 1926

There are also grave doubts concerning the presence of the factor of catabolism of sugar in muscles in diabetes. Beattie and Milroy¹⁵ report almost no difference between the muscles of normal and of diabetic patients in this respect. Lange's¹⁶ work also tends toward this belief. He was not able to detect marked differences in the sugar metabolism of the muscles of normal and of diabetic patients in the production of lactic acidogen. Griffith's¹⁷ experiments showed that epinephrine also had no effect on the lactic acid or total acid product by muscle and probably therefore on the utilization of carbohydrate.

It is common knowledge that the action of insulin is prevented by infections. In the treatment of diabetes, the intervention of a boil, gangrene or a respiratory infection will often cause the complete loss of carbohydrate tolerance in spite of large doses of insulin. Cardiovascular disturbances also are known to give rise to resistance to the action of insulin. This was first called to our attention by Wilder¹⁸. The mechanism of this inhibition has never been understood. The suggestion by Schiff and Cholemis that alkalosis is a factor cannot well be accepted, as it is well known that in many of these conditions acidosis is the rule. It also is the experience of most surgeons that there may be failure of the action of insulin in the absence of acidosis even comparable to that observed in patients with severe diabetes who react promptly to insulin. Lawrence¹⁹ has said that toxemias will inhibit the hypoglycemic effect of insulin. He used diphtheria antitoxin in his experiments. We have been unable to confirm these results. Chart 6 shows the effect on the insulin curve of the injection of a number of toxic substances. These include suppurative material of several kinds. We purposely included the material from limbs rendered gangrenous by ligation of a vessel as a parallel to diabetic gangrene. *Bacillus coli* and staphylococcus cultures also failed to inhibit the effect of insulin, except in enormous doses such as give rise to severe anaphylactic shock. In several cases we used toxins of various sorts of such overwhelming nature as to cause death in from three to four hours, but inhibition of the insulin hypoglycemia could not be demonstrated.

15 Beattie, F., and Milroy, T. H. Role of Phosphates in Carbohydrate Metabolism, *J Physiol* **62** 174 (Dec 10) 1927

16 Lange, H. Lacticidogen Metabolism in Diabetic Muscle, *Arch f exper Path u Pharmacol* **113** 115 (Nov) 1926

17 Griffiths, F. R. The Metabolic Effect of Adrenalin on Frog's Muscle, *Am J Physiol* **65** 15 (June) 1923

18 Wilder, R. M. Clinical Assaying of Insulin and the Insulin Requirement, *Endocrinology* **8** 630 (Sept) 1924

19 Lawrence, R. D. Inhibition of Insulin Action by Toxemias, *Brit M J* **11** 983 (Nov 27) 1926

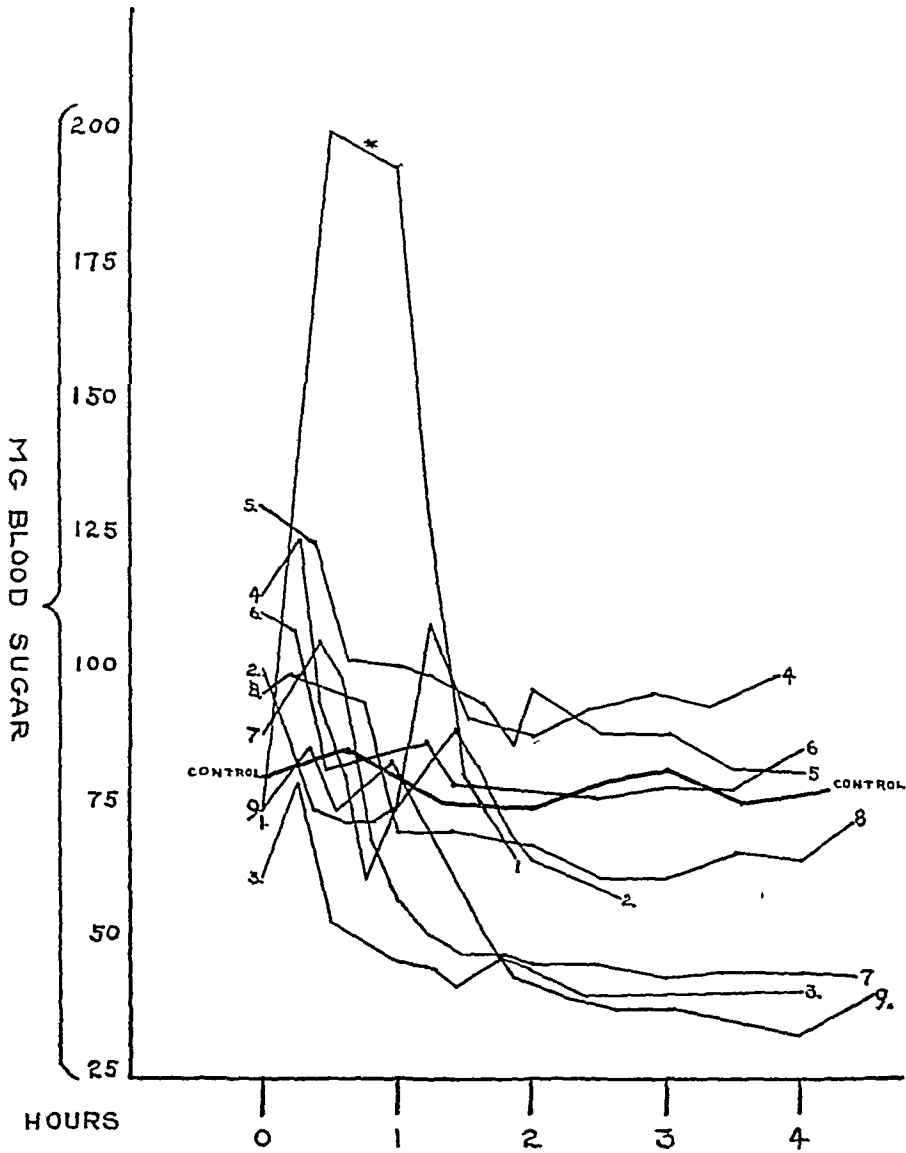


Chart 6—The effect of various toxic substances on the insulin curve of normal dogs, insulin was given in all cases at 0 time 1 is a curve showing the effect of one-half unit of insulin per kilogram of body weight and 100 mg of *B coli* given intravenously at the point indicated by the asterisk The dog died 2 is a curve showing the effect of one-half unit of insulin per kilogram of body weight and 1 cc of extract of necrotic skin, only proteins, 3, the effect of one-half unit of insulin per kilogram and 1 cc of whole extract of necrotic skin, 4, the effect of one-half unit of insulin per kilogram and 1 cc of whole extract of necrotic skin given intravenously, 5, the effect of one-half unit of insulin per kilogram and 0.5 Gm of cholesterol given intravenously, 6, the effect of one-half unit of insulin per kilogram and 0.5 cc of heavy culture of dead staphylococci, 7, the effect of one-half unit of insulin per kilogram and 0.5 cc of whole pus taken postoperatively from a dog with empyema, 8, the effect of one-half unit of insulin per kilogram and all of the iodized oil from 300 cc of pus taken postoperatively from a dog with empyema, injected intravenously in 2 cc of watery emulsion and 9, the effect of one-half unit of insulin per kilogram and 0.5 Gm of cholesterol given one hour before the experiment

Injections of cholesterol in enormous doses were also tried, as we thought that the hypercholesterinemia of vascular disease might be a factor, but, as can be seen, their effect was nil. In this connection it is interesting to note Mahler's²⁰ experiments, which show that insulin prevents the hypercholesterinemia of ether anesthesia but has no effect on that of diabetes.

What, then, is the explanation of the phenomenon with which this article is concerned? The only clue to the problem yet discovered is in the work of Foster.²¹ He showed that if a given amount of sugar is fed to a patient, there is a definite rise in the blood sugar, but that if the dose is repeated within a short period, this rise is much less and often is absent. In fact, an actual hypoglycemia may result. He also showed that there is a marked hypoglycemia following the initial rise after the ingestion of large doses of dextrose. He explains these reactions on the basis that the carbohydrate metabolism has been speeded up by the first dose and is going on at such a rate that the second dose is easily stored or consumed without giving rise to hyperglycemia. It is well known that in dehydrated animals the metabolism is speeded up, not only is the metabolic rate higher, but all the metabolic changes are proceeding at a higher rate. Nitrogen waste is also increased. One might therefore assume that in our animals the consumption of carbohydrate was already proceeding at a higher rate in the dehydrated dogs, and therefore the fall in blood sugar was more marked.

Finally, in this connection, it is interesting to note the fact recently observed by Olmsted,²² Edwards²³ and many others that insulin has the effect of markedly concentrating the blood. This secondary action, of course, acts as a marked adjuvant to its hypoglycemic function.

CONCLUSIONS

1 In diabetic animals the hypoglycemic effect of insulin is enormously exaggerated and prolonged in anhychemia and lessened or abolished in hychemia.

2 In normal and diabetic animals, hydration or dehydration has no effect on the daily blood sugar curve unless insulin is injected.

20 Mahler, A. Blood Cholesterol During Ether Anesthesia, *J Biol Chem* **69**.653 (Aug.) 1926.

21 Foster, G. L. Studies in Carbohydrate Metabolism, II. *J Biol Chem* **55**.303 (April) 1923.

22 Olmsted, M. D. Effect of Insulin on Blood, *Am J Physiol* **69** 137 (June) 1924.

23 Edwards, D. J. Production of Anhydremia with Insulin, *Am J Physiol* **70**.273 (Oct.) 1924.

3 Intoxications of various sorts do not have an inhibitory effect on the action of insulin

4 A possible explanation for these phenomena is offered, but further work on the subject is highly desirable

5 The degree of hydration of the body must be considered in the use of insulin, especially in diabetic subjects, in order to avoid hypoglycemic reactions

MATERIAL FROM LYMPH NODES OF MAN

II STUDIES ON LIVING AND FIXED CELLS WITHDRAWN FROM LYMPH NODES OF MAN¹

CLAUDE ELLIS FORKNER, M D

BOSTON

In a previous paper I described a simple method for obtaining living cells from lymph nodes or tumors

Particular stress has been placed on the study of living cells, because one not only obtains from them a true cytologic picture, but also can observe them in their physiologic behavior to altered environmental conditions. Apparently most of the work on the pathology of lymph nodes has been concerned chiefly with their altered architecture and their grosser histology. Dr. George R. Minot suggested to me that a study of the fresh cells of lymph nodes might be worth while, and from former work I believed that a closer scrutiny of cell organs, such as mitochondria, specific granules, segregation bodies and other cytoplasmic and nuclear structures, not only in fixed preparations, but also with special reference to the pathologic physiology and histology of these organs in living cells, might provide valuable information. It was with the idea of studying living cells freshly drawn from diseased tissue that the studies of pathologic lymph nodes reported here were undertaken. Further studies on the cytology of tumors is in progress and will be presented at a later date.

MATERIAL STUDIED

The method described¹ has been applied to the study of thirty cases² of lymph node disease in which thirty-eight punctures were performed. Twenty-three patients have had punctures of their lymph nodes, the remaining cases were studied by puncture of biopsy material. A pathologic report was made on the sectioned tissue in all but six cases and two of these showed the classic blood picture of chronic lymphatic leukemia. In most instances the sections were

¹ From the Medical Service of the Collis P. Huntington Memorial Hospital of Harvard University.

¹ Forkner, C. E. A Method to Obtain Material by Puncture of Lymph Nodes for Study with Supravital and Fixed Stains, Arch. Int. Med., p. 532, this issue.

² Some of these cases were studied at the New England Deaconess and New England Baptist Hospitals.

studied by Dr J Homer Wright A few reports were made by Dr Lawrence W Smith These pathologic reports, together with my studies on many lymph nodes obtained from fresh autopsies in which there was no apparent pathologic process of the lymphatic system, have furnished adequate controls

NORMAL LYMPH NODES

The cellular content of normal retroperitoneal and deep cervical nodes showed similar cytologic characteristics, which were practically constant in all the cases studied The picture was dominated by the presence of many lymphoid cells, which comprised about 90 per cent, and which were found in various stages of development Almost all of these cells were small and had round nuclei and moderate amounts of cytoplasm³ (fig 1) The cytoplasm usually did not contain structures staining with neutral red Most of the cells had a few small globular or rod-shaped mitochondria, which frequently were grouped in one or two colonies in the cytoplasm near the nucleus The mitochondria stain a delicate bluish green with the janus green These cells were undoubtedly immature lymphocytes, for as Sabin⁴ has pointed out, the mature lymphocyte almost invariably contains one or more cytoplasmic structures staining with neutral red, is small and has a narrow cytoplasmic ring containing grouped perinuclear mitochondria Although many of these cells tend to show a grouping of the mitochondria, which characteristic is considered evidence of maturation and differentiation toward the adult cell type, there are a large number in which these Altman bodies have no characteristic distribution, but are diffusely scattered throughout the cytoplasm Cunningham, Sabin and Doan⁵ have shown that those lymphoid cells which do not possess neutral red bodies, and which possess mitochondria, either diffusely scattered or with a beginning grouping around the nucleus, are best considered as lymphoblasts

The cells of the lymphoid series comprised over 90 per cent of all the cells present in material obtained by puncture of normal lymph

3 The figures which accompany this paper have in some instances been made from fixed preparations rather than from supravitaly stained ones This is because it was often impossible to secure the services of the artist when the living cells had just been withdrawn, which is the best time to observe them

4 Sabin, F R Studies on Living Human Blood Cells, Bull Johns Hopkins Hosp **34** 277, 1923

5 Cunningham, R S Sabin F R, and Doan, C A The Development of Leucocytes, Lymphocytes, and Monocytes from a Specific Stem-Cell in Adult Tissues pub 361 Contribution to Embryology 84 Carnegie Inst, Washington, 1925 p 227

nodes The remaining cells, approximately 10 per cent, were made up of reticular cells, fibroblasts, macrophages, occasional histogenous mast cells, occasional polymorphonuclear leukocytes and another cell the identity of which I have not yet determined

The reticular cells found in bone marrow and lymph nodes have been studied by Cunningham, Sabin and Doan⁵ They described these cells as occurring characteristically in groups and having irregular cytoplasmic borders, the cytoplasm appearing like smooth ground glass, and containing no structures staining with neutral red or janus green They regard these cells as the precursors of all the white blood cells In the films which I have studied of living cells from normal lymph nodes, these reticular cells were found in small numbers, varying from 0.5 to 4 per cent The cytoplasm usually was nongranular, and its borders could be defined only with scrutiny The nucleus was large, oval or round with the chromatin rather diffusely scattered (fig. 2)

In studying many smears of normal lymph nodes cells were found frequently which resembled fibroblasts in all of their characteristics They were usually elongated cells with an oval nucleus and branching cytoplasm containing few or no granules Delicate mitochondria staining a light blue were seen occasionally in the cytoplasm

Another cell which was seen in relatively small numbers in lymph nodes is the characteristic clasmatocyte or macrophage Normally, these cells are scarce, but in certain pathologic cases to be mentioned later, they occur in considerable numbers These clasmatocytes were conspicuous by their large size and by the presence in their cytoplasm of huge granules or vacuoles staining with natural red The granules or vacuoles varied markedly and increased perceptibly in size with longer exposure to the neutral red The vacuoles varied in their coloring, some of them were a bright red giving the acid reaction of the dye, while others were more of an orange yellow, giving the basic reaction Neutral red is not only a specific stain for these cytoplasmic vacuoles, but it also enables one to tell something of their reaction, for the granules on the acid side of pH 6.8 are stained red, while those on the basic side of pH 7.8 are stained yellow or orange The clasmatocytes or macrophages frequently showed changes in shape and exhibited some degree of motility, although the number and size of the vacuoles apparently was not dependent on this factor Mitochondria were not conspicuous in these cells, but on careful observation one could see them scattered diffusely in the cytoplasm, appearing as delicate filaments and rods staining lightly

with the dilute janus green. The nuclei are usually round and do not stain in supravital preparations.

Normal lymph nodes sometimes showed typical histogenous mast cells which could not be confused with any other type of cell found. They were characterized by an abundance of deeply basophilic granules of equal size which filled the cytoplasm and tended to obscure the small, centrally placed, round nucleus. These cells were not numerous, but it must be borne in mind that they do occur in normal lymph nodes of man.

Occasionally one sees also the typical active, migrating neutrophilic polymorphonuclear leukocytes with fine refractive granules of equal size, staining lightly a delicate orange, or if the dye is dilute, there may be no perceptible staining. These cells may or may not contain one or several reddish vacuoles in their cytoplasm.

It is of interest to note at this point that in nodes obtained at autopsy it was not possible to identify definitely monocytes or the so-called endothelial leukocytes. The supravital technic is an admirable method for the identification of these cells, it would seem from the evidence at hand that normally they have no place in lymph nodes. This point has been particularly noted because of the existing controversy about the origin and presence of monocytes in lymph nodes.⁶

At times I found still another cell in apparently normal lymph nodes. This cell was large and possessed one or more nuclei. It was conspicuous by the presence of very large refractive granules which were considerably larger than the specific granules of polymorphonuclear eosinophilic leukocytes, and which did not stain with vital dyes. The cells were irregular in shape and varied in size from that of a large neutrophil to a cell several times as large. The large granules did not increase or decrease in size, tended to fill the whole cytoplasm and were soluble in both water and alcohol. Their origin or their place in the histology or physiology of lymph nodes is not clear, and further study is required on this point.

PATHOLOGIC LYMPH NODES

The term lymphoblastoma (Mallory) is used in this paper to include the following conditions sharply separated from each other by certain pathologists, lymphatic leukemia, lymphosarcoma, Hodgkin's disease and aleukemic lymphatic leukemia (pseudoleukemia).

⁶ For a further discussion on the origin of the monocytes in lymph nodes the reader is referred to the article of McJunkin, F. A. Origin of Mononuclear Phagocytes of Peritoneal Exudates. *Am J Path* 1:305, 1925.

Table 1 gives a list of the conditions studied, together with the diagnoses ⁷ made in the clinic, those made by routine pathologic section and those made by puncture. The diagnoses arrived at from study of material obtained by puncture was made prior to learning the diagnoses made from the sectioned tissues.

BENIGN HYPERPLASIA

The cases which showed least variation from normal were simple hyperplastic nodes resulting from nearly infection with common organisms. Many nodes have been examined which were enlarged as the result of a terminal septicemia and many others near the hilum of the lung. Such cases did not present an abnormal percentage of immature atypical cells, nor did the proportion of cells found vary from that of the normal node except for the presence of many more of the polymorphonuclear leukocytes. The latter cells were easily recognized by their histologic characteristics and by their active motility in fresh preparations.⁸ There was not the preponderance of young cells showing evidence of rapid proliferation which one finds in lymphoblastoma.

LEUKEMIA

Leukemia, lymphatic leukemia and aleukemic leukemia probably cannot be differentiated by material obtained from puncture of lymph nodes, for in both of these conditions the pathologic process is well known to be entirely similar. However, if one observes the lymphoid cells carefully in these conditions, it is apparent that although they are the size of adult lymphocytes there is an absence of the other characteristics of cellular differentiation so evident in cells of normal lymph nodes. Only a few of the cells in the leukemic nodes contained any grouping of the mitochondria, and almost none of them contained the cytoplasmic granules staining with neutral red. The nucleus was also characterized by a diffuse scattering of the chromatin rather than by an aggregation in masses as occurred in a large proportion of the normal lymph node cells. In lymphatic leukemia, with or without a leukemic blood picture cells obtained by puncture were of a more or less uniform immature type in distinction to the greater number of more differentiated cells of normal lymph nodes. This is also to be observed in sections of fixed tissue.

⁷ When a diagnosis was rendered in a name different from that used in this paper it has been given here in the terminology adhered to in this communication.

⁸ Excellent descriptions of living blood cells stained by the supravital method are given in the articles of Sabin and Simpson referred to in the bibliography of this and the preceding paper.

TABLE 1—Data Concerning Cases Studied by Puncture of Lymph Nodes

Case No	Age	Sex*	Pathologic Diagnosis	Preliminary Clinical Diagnosis	Diagnosis by Puncture	Biopsy † Puncture or Clinical Puncture	Duration of Adenopathy	Location of Tumor Punctured	Number of Punctures
1	36	♂	Lympho- blastoma (Hodgkin's)	Lympho- blastoma (aleukemic leukemia)	Lympho- blastoma, (leukemic)	Clinical	3½ years	Right Posterior part of Neck	1
2	36	♂	Doubtful lympho- blastoma	Lympho- blastoma	Lympho- blastoma	Biopsy	1¾ years	Neck	1
3	22	♂	Lympho- blastoma	Lympho- blastoma	Hodgkin's	Clinical	2¾ years	Neck	2
4	61	♂	Lympho- blastoma (sclerosing ‡)	Lympho- blastoma	Hodgkin's	Clinical	1½ years	Neck	1
5	29	♀	Lympho- blastoma (Hodgkin's)	Lympho- blastoma	Hodgkin's	Clinical	7 years	Neck	2
6	37	♂	Lympho- blastoma (sclerosing)	Lympho- blastoma	Hodgkin's	Clinical	1½ years	Neck	1
7	54	♂	Lympho- blastoma	Lympho- blastoma (rapidly growing)	Lympho- blastoma (rapidly growing)	2 Clinical 1 Biopsy	3 years	Neck	3
8	36	♂	Lympho- blastoma (Hodgkin's)	Lympho- blastoma	Hodgkin's	1 Clinical 1 Biopsy	½ year	Neck	2
9		♀	Lympho- blastoma	? Hodgkin's	Lympho- blastoma (rapidly growing)	Biopsy		Neck	1
10	18	♂	No Lympho- blastoma in specimen	Lympho- blastoma	Lympho- blastoma	Biopsy	1 year	Neck	1
11	13	♂	Sarcoma with ? of angio- sarcoma	Lympho- blastoma	Lympho- blastoma	Clinical	1½ year	Neck	1
12	54	♀	None	Chronic lymphatic leukemia	Lympho- blastoma (leukemia)	Clinical	5 years	Neck	1
13	61	♀	Lympho- blastoma	Chronic lymphatic leukemia	Lympho- blastoma (leukemia)	Clinical	2¾ years	Neck	1
14	51	♂	None	Chronic lymphatic leukemia	Lympho- blastoma (leukemia)	Clinical	1¼ years	Axilla	1
15	18	♀	Leiomyo- sarcoma	Tubercu- losis	Fibroma	Biopsy	2 weeks	Neck	1
16	16	♀	Benign hyper- plasia	Lympho- blastoma of tonsil	Benign hyper- plasia with in- fection	Biopsy	3 years	Tonsil	1
17	66	♂	Adeno- carcinoma	Lympho- blastoma (Hodgkin's)	Carcinoma	2 Clinical 1 Biopsy	½ year	Neck	3
18	17	♂	Epithelial carcinoma	Lympho- blastoma (Hodgkin's)	Carcinoma	Clinical	1¼ years	Neck	2
19	48	♂	None	? Of carcino- ma or lympho- blastoma	Carcinoma	Clinical	1 year	Neck	1
20	58	♂	None	Lympho- blastoma	Carcinoma	Clinical	2 years	Neck	1
21	30	♀	Adeno- carcinoma	Lympho- blastoma (Hodgkin's)	Carcinoma	Biopsy		Axilla	1
22	45	♀	Carcinoma	Carcinoma	Carcinoma	Biopsy		Axilla	1
23	50	♀	Carcinoma	Carcinoma	Carcinoma	Biopsy		Axilla	1
24	29	♀	Tubercu- losis	Tubercu- losis	Tubercu- losis	Biopsy	4 years	Neck	1

* In this table ♂ indicates male ♀ female

† By biopsy puncture is meant puncture of tissue removed at operation in distinction to clinical punctures which were performed on patients independent of other procedures

‡ Sclerosing lymphoblastoma is a term used to indicate the picture seen in a section of relatively far advanced Hodgkin's disease

TABLE 1—Data Concerning Cases Studied by Puncture of Lymph Nodes—Continued

Case No	Age	Sex*	Pathologic Diagnosis	Preliminary Clinical Diagnosis	Diagnosis by Puncture	Biopsy † Puncture or Clinical Puncture	Duration of Adenopathy	Location of Tumor Punctured	Number of Punctures
25	29	♂	Tuberculosis	Lymphoblastoma	Tuberculosis	Biopsy	1½ years	Neck	1
26	32	♂	Tuberculosis	Tuberculosis	Tuberculosis	Biopsy	3 years	Neck	1
27	49	♂	Tuberculosis	Tuberculosis	Tuberculosis	Biopsy	2 years	Neck	1
28	23	♀	Tuberculosis	Tuberculosis	Tuberculosis	Biopsy	3 years	Neck	1
29	41	♀	Tuberculosis	Tuberculosis	Tuberculosis	Clinical	15 years	Neck	1
30	8	♂	None	? Of Tuberculosis or Lymphoblastoma	Tuberculosis	Clinical	2½ years	Neck	1
31	21	♀	Tuberculosis	Lymphoblastoma	Tuberculosis	Clinical	1 month	Neck	1

HODGKIN'S DISEASE

Steinberg,⁹ Reed,¹⁰ Longcope¹¹ and others have established a more or less characteristic histologic picture for what is ordinarily termed Hodgkin's disease, and Mallory¹² refers to the condition as a sclerosing type of lymphoblastoma. The early stage of the condition is characterized by a proliferation of lymphoid cells, which is then followed by the appearance of many larger and paler cells with vesicular, palely staining nuclei. The latter structures have been called endotheloid cells. Among the so-called endotheloid cells are found other larger cells with pale, irregular cytoplasm containing one or several large, rounded or indented nuclei which usually lie adjacent to each other. These nuclei each contain one or two nucleoli. Many eosinophils are also not infrequently found. After a time, however, the cellular picture tends to be replaced by a progressive scar formation throughout the node, leaving areas of cellular proliferation here and there.

The material obtained by puncture of lymph nodes in Hodgkin's disease at a relatively advanced stage revealed the same cytologic characteristics that were found in sections of such nodes. Some of the advanced cases with marked sclerosis of the tumor masses showed fewer cells than earlier in the disease. The large, pale cells showing the char-

9 Sternberg, C. Universelle Primärerkrankungen des lymphatischen Apparates, *Centralbl f d Grenzgeb d Med u Chir* 2 641, 1899, Ueber eine eigenartige unter dem Bild der Pseudoleukämie verlaufende Tuberculose des lymphatischen Apparates *Ztschr f Heilk* 19 21, 1896.

10 Reed, D. M. On Pathological Changes in Hodgkin's Disease, with Especial Reference to its Relation to Tuberculosis, *Johns Hopkins Hosp Rep* 10 133 1902.

11 Longcope, W. T. Pathological Histology of Hodgkin's Disease, with a Report of a Series of Cases *Bull Ayer Clin Lab* 1 4, 1903.

12 Mallory, Frank B. Principles of Pathologic Histology, Philadelphia, W B Saunders Company 1915.

acteristics of reticulum cells were abundant. In these cells mitotic figures were not infrequently seen, but rarely could mitochondria be observed in the cytoplasm. Certain cases of rapidly advancing Hodgkin's disease showed these reticulum cells containing irregular sized particles in the cytoplasm, staining with neutral red and in this manner resembling the reticulum cells seen in other cases of rapidly growing lymphoblastoma. In addition giant cells with delicate irregular cytoplasm containing one or several oval or indented nuclei could be observed. In most instances eosinophils were present containing large yellow refractive granules in the cytoplasm. Macrophages were sometimes seen and fibroblasts were almost always present, but they were more abundant in the late cases in which there were hard, sclerosed nodes.

RAPIDLY PROGRESSING LYMPHOBLASTOMA

In rapidly growing lymphoblastoma other than Hodgkin's disease and lymphatic leukemia, the nodes often were soft and showed a cellular picture. Likewise, these cases progressed rapidly to death. There was marked variation in the types of cells found in distinction to the cytologic picture of chronic lymphatic leukemia, in which the cells were apt to be about the same size and more uniform in character. In these rapidly progressing cases the cells exhibited numerous mitotic figures (fig 3). Many large, pale cells resembling reticulum cells were present in the smears (fig 4). All sorts of abortive immature lymphocytes were found, which contributed largely to the picture (fig 5). They varied from large cells with diffusely scattered mitochondria and no cytoplasmic neutral red bodies in a rather abundant cytoplasm, to the small, more adult lymphocyte which was practically completely differentiated. The adult lymphocytes were much less abundant than in normal nodes.

The various cells removed from normal lymph nodes, from the nodes in chronic lymphatic leukemia with or without a leukemic blood picture and from the rapidly progressing lymphoblastoma varied in size, the cells from the lymphoblastoma were obviously larger than the normal or the leukemic cells. If one should plot a frequency curve of the diameters of the cells, in much the same manner as Price-Jones has done in plotting the sizes of red blood cells, there would be a more marked variation in size and a distinctly larger mean diameter of the cells from rapidly progressing lymphoblastoma than those from normal or leukemic nodes. The leukemic cells would show a mean diameter intermediate between that of the normal node cells and the cells from rapidly growing lymphoblastoma. However, the difference in size of cells in normal lymph nodes, chronic lymphatic leukemia and rapidly progressing lymphoblastoma is probably of less importance than are the finer cytologic characteristics described.

It would appear from this discussion that the study of cells from puncture of lymph nodes provides certain definite histologic evidence for the separation of enlargement of the lymph node due to (a) benign hyperplasia, (b) chronic lymphatic leukemia with or without a leukemic blood picture, (c) Hodgkin's disease and (d) other lymphoblastomas of rapidly growing type, which many pathologists might perhaps call lymphosarcoma.

CARCINOMA

The material obtained by puncture of carcinomatous nodes in seven patients appeared different in all instances from that collected from cases of lymphoblastoma. It was thus possible to distinguish not only different sorts of lymphoblastoma, but also to separate clearly this group of cases from those with metastatic carcinoma. Case 19 (table I), is illustrative. Clinically, the case appeared to be one of typical Hodgkin's disease, but a study of the cells withdrawn by puncture of a huge mass of tissue on the left side of the neck revealed a histologic picture distinct from that encountered in Hodgkin's disease. In this case the cells were all of the same type, large in size and often occurred in groups of half a dozen or more, separated by poorly defined borders. Many isolated cells with an irregular rounded contour were also present. These showed an abundance of rather dense ground-glass-like cytoplasm and a huge nucleus containing a well defined nucleolus (figs 6, 7, 8 and 9). The nucleoli were refractive and seemed to give a delicate basic reaction to neutral red. Neither mitochondria nor cytoplasmic structures staining with neutral red were detected, however, the cells, including the nucleus, became a delicate pink when a slightly concentrated solution of neutral red was used. Ameboid activity was not observed. The cells were classic examples of those found in cancer, and the tumor was undoubtedly a carcinoma, as shown by a study of the tissue obtained at biopsy.

There were four types of tumor cells among the seven cases. The different kinds of cells resembled each other in their general characteristics but differed in finer details. The cells were alike for any given tumor. In three cases they were identical histologically. There were other cases among the seven, in addition to the one already cited, in which the clinical diagnoses were in doubt, but which were proved to be carcinoma. In two of these cases there were solitary nodes deep in the neck and situated so that their surgical removal was considered too difficult to undertake. However, they were readily punctured, and the material contained cells typical of cancer, thus the value of this procedure is illustrated.

TUBERCULOSIS

Eight cases of tuberculosis of the lymph nodes were studied, and the observations appear to indicate that cellular material withdrawn from

such nodes has distinctive characteristics, so that puncture of lymph nodes can aid in distinguishing tuberculosis from other disorders of the lymphoid tissue. The films of cells obtained from nodes proved to be tuberculous contained a generous proportion of the so-called epithelioid cells, which tend to dominate the histologic picture of tuberculosis. Sometimes they constituted about 85 per cent of all the cells removed. Lymphocytes, mostly of the small, well differentiated type with perinuclear mitochondria, were more abundant in some cases than in others, but the epithelioid cells were a distinguishing feature of the material obtained from tuberculous lymph nodes. These large cells were usually oval, with a relatively small vesicular nucleus and cytoplasm that appeared very finely granular and possessed a faint but distinct yellowish tinge which could be seen in both the stained and unstained preparations. The epithelioid cells often contained more than one nucleus, and occasionally one could be distinguished that appeared transitional from the simple epithelioid cells to typical giant cells with numerous nuclei grouped near the periphery. Simple epithelioid and typical giant cells do not contain cytoplasmic granules staining with neutral red, and in only a few instances were structures resembling mitochondria made out. The giant cells in the smears from tuberculous lymph nodes in most instances differed from those encountered in Hodgkin's disease in several ways. The giant cells of Hodgkin's disease contained a large irregular, bilobed, or in many cases a multiple lobed, nucleus. The nuclei of tuberculous node giant cells were numerous, small and lay scattered near the periphery of the cell, whereas the nucleus or nuclei of Hodgkin's giant cells were large, well defined, irregular bodies lying close together, and often centrally placed. These observations are in agreement with the general observations in fixed tissue and with the observations of McJunkin¹³ on the character of the giant cells in Hodgkin's disease. McJunkin studied these cells by injecting lymph nodes.

Macrophages almost invariably were present in the material from tuberculous lymph nodes. They were slightly motile, and contained in the cytoplasm numerous irregular bodies staining with neutral red and varying in size from barely perceptible granules to bodies even larger than red blood corpuscles. A few polymorphonuclear neutrophils and an occasional mast cell usually could be seen. In a few instances there occurred large cells with one or more nuclei and with cytoplasm that was filled with huge refractive, nonstaining granules. This type of cell was described in the early part of this paper as occasionally occurring in normal lymph nodes, but its identity is not known. Material from

¹³ McJunkin F. A. Supravital Reaction to Neutral Red of the Cells of Lymph Nodes of Hodgkin's Disease, *Arch Path* 2:815 (Dec) 1926.

the tuberculous lymph nodes also often contained a considerable number of dead degenerating cells and cellular debris

Isolated observations were made in a few cases of other diseases than those already given, for example, the nodes in a case of myelogenous leukemia were punctured, and the cell content was the sort to be expected in this disease

Tables 2 and 3 present an outline of the chief characteristics and differences in the cytologic pictures of the various groups of lymph node diseases studied by means of puncture

TABLE 2—*Chief Cytologic Characteristics of Material Removed by Puncture of Lymph Nodes*

Normal Lymph Nodes	Benign Hyperplasia	Tuberculosis	Carcinoma
1 Dominated by cells of lymphocytic series	1 Lymphocytic cells of same type and number as those in normal lymph nodes	1 <i>Epithelioid cells</i> often oval with small vesicular nucleus and abundant very finely granular cytoplasm which has a light yellow tinge in unstained and supravital preparations	1 Cells almost entirely of one type, large oval or angular cells with pale non granular but often finely vacuolated cytoplasm, oval or round nucleus with nucleolus
a Early lymphoblasts, few in number, very basophilic cytoplasm, diffusely scattered mitochondria, diffusely scattered chromatin in nucleus	2 Reticular cells as in normal nodes	2 Macrophages usually present, often more than normal or in benign hyperplasia	2 Conspicuous absence of lymphoid cells and of the other normal constituents of lymph nodes
b Lymphoblasts of later stage, relatively many (30-40%), narrow cytoplasmic ring, grouped perinuclear mitochondria, no cytoplasmic neutral red bodies	3 Fibroblasts as in normal nodes	3 Neutrophils usually present, often more than in normal nodes	
c Lymphocytes practically completely differentiated, relatively many (40-50%), grouped perinuclear mitochondria, one or more neutral red bodies	4 Macrophages increased in number	4 Often degenerating cells and cellular debris, caseous material often is withdrawn	
2 Reticular cells, few in number	5 Histiogenous mast cells frequently	5 Giant cells with multiple small nuclei around periphery of cell in contrast to the usual large irregular centrally placed nucleus or nuclei in giant cells of Hodgkin's disease	
3 Fibroblasts, infrequent	6 Increased numbers of polymorphonuclear neutrophils as compared to normal lymph nodes	6 Tubercle bacilli rarely found	
4 Macrophages, rare	7 Giant cells as in normal nodes		
5 Histiogenous mast cells, rare	8 Eosinophils are often present but are not a conspicuous feature		
6 Polymorphonuclear neutrophils, rare			
7 Giant cell with huge refractive granules not staining with vital dyes, rare			

COMMENT

From study of the tables 2 and 3, it will be apparent that there are definite histologic differences in the cells of the diseases discussed. Benign hyperplasia and tuberculosis do not show the atypical development of lymphoid cells which is present in the lymphoblastoma group. Benign hyperplasia is distinguished by the fact that there is no disturbance in the general cytologic picture, but there is an increase in the polymorphonuclear elements. Given a smear of material from a lymph node in which there is no evidence of altered cellular development, and

with an increase of the cells ordinarily found in sites of chronic inflammation, one is justified in making a diagnosis of benign hyperplasia

Tuberculosis is readily distinguished by the presence of so-called epithelioid cells, and their character is distinctive. Disintegrated cells also are features of tuberculosis

Carcinoma is apparent at a glance, and no differential cytologic diagnosis need be discussed. The cells are characteristic, as indicated in the tables

TABLE 3—*Chief Cytologic Characteristics of Material Removed by Puncture of Lymph Nodes*

Lymphoblastoma		
Chronic Lymphatic Leukemia With or Without Leukemic Blood Picture	Hodgkin's Disease	Rapidly Progressing Lymphoblastoma Other Than Leukemia and Hodgkin's Disease
1 Cells of lymphatic series dominate picture, relatively few differentiated lymphocytes; number of poorly differentiated cells with diffusely scattered mitochondria and a relatively large amount of cytoplasm is much larger in this group than in normal, cells of uniform immature type, mitotic figures more frequent than normal, less frequent than in the rapidly progressing lymphoblastoma	1 Presence of large pale endothelioid cells in considerable numbers; no characteristic color to cytoplasm in contrast to characteristic yellowish tinge of epithelioid cells of tuberculosis, nucleus is large in contrast to small nucleus of epithelioid cells of tuberculosis	1 Marked increase over normal of the reticular cells
2 Reticular cells, few in number	2 Large giant cells with one or more large distinct, vesicular, irregular, usually centrally placed nuclei are characteristic	2 All types of typical and atypical early lymphoblasts with abundant cytoplasm, cells frequently much larger in size and more irregular in shape than in leukemia
3 Almost complete absence of other structural elements	3 Eosinophils often very abundant, usually more than in other diseases, not always the case, for there may be few or none present, especially in early cases	3 Mitotic figures conspicuous and more abundant than in any other type of lymphoblastoma
	4 Macrophages rare	4 Almost total absence of differentiated lymphocyte
	5 Lymphoid cells present in considerable numbers in early cases, fewer in advanced cases	5 The large giant cells seen in normal nodes are more numerous in these cases
	6 Fibroblasts numerous in advanced cases, few in early cases	

Lymphoblastoma in general is characterized by an atypical developmental process, and it is this feature more than any other which causes it to be set apart from the other lymph node diseases. It is in lymphoblastoma that one finds an ungoverned tendency to rapid proliferation of cellular elements which when carried to the extreme produced a picture that one can scarcely recognize as altered lymphoid tissue

Chronic lymphatic leukemia, with or without a leukemic blood picture, is characterized by the great preponderance of uniformly immature lymphoblasts, whereas the reticular cells and stroma cells are only slightly, or not at all, involved in the process. On the other hand, in Hodgkin's disease although it also is characterized by lymphoid proliferation, especially in the early stages, the striking feature is the

increase in stroma tissue together with the presence of peculiar endothelial cells and eosinophils

The third type of lymphoblastoma has been referred to as rapidly progressing. Here the striking changes are not in the stroma or in the lymphoblasts, both of these elements, it is true, show changes, but the striking change is in the great increase of reticular cells and the presence of many atypical forms which are probably early lymphoblasts

EFFECT OF THE ROENTGEN RAY

A few nodes were punctured soon after roentgen-ray treatments. Material taken from a carcinoma three hours after treatment showed many cells with vacuoles and fragmentation of the cytoplasm (fig 10). There was considerable cellular debris, and huge macrophages or clasmatocytes migrated about with brilliantly stained granules and vacuoles of many different sizes and shapes. These granules varied in color from red to various shades of brown and yellow. Puncture of the same tumor mass a few days prior to therapy did not show evidence either of cellular degeneration or of phagocytosis. Another case was diagnosed as a rapidly growing lymphoblastoma. Before treatment, the cells from a diseased node showed many mitotic figures, a few hours after deep roentgen-ray irradiation (500 electrostatic units), cells obtained by puncture of the same node did not show any mitotic figures, but the number of macrophages had increased, and many more cellular fragments were present than before therapy.

BACTERIOLOGIC AND PARASITOLOGIC STUDIES

Smears of the material obtained from each case of tuberculosis were fixed and stained for acid-fast organisms, in only one instance were they found. Diligent search for acid fast organisms in preparations from lymphoblastoma was without reward. Fresh films from many of these cases were examined by aid of the dark-field microscope. In no instance were spirochetes observed, which is contrary to the observations of White and Proscher.¹⁴ Dr W. C. Boeck made observations to determine whether or not amebas were present in the material from many of the cases of lymphoblastoma, but none was identified.

SUMMARY AND CONCLUSIONS

The study of living and fixed cells withdrawn from lymph nodes of man is of value. Material withdrawn on the barbs of a dental broach has been studied by the supravital method, by dark-field examination and by fixed stains.

¹⁴ White, W. C., and Proscher, F. Spirochaetes in Acute Lymphatic Leukemia and in Chronic Benign Lymphomatosis, *J. A. M. A.* **49** 1115 (Sept 28) 1907.

This method provides one with information, quickly and easily obtained, concerning the cytology, bacteriology and pathologic physiology of the disease process. The observations reported here are few, and thus do not permit unequivocal statements. Many more cases must be studied before a final estimate of such observations can be made.

The cases studied include different types of lymphoblastoma, tuberculosis, benign hyperplasia and carcinoma. Control examinations of normal nodes were also made. These conditions each gave a distinctive cytologic picture, the salient features of which are set apart in italics in tables 2 and 3.

Puncture of lymph nodes provides a way to follow the spontaneous morphologic changes in disease and those induced by treatment. Likewise, prognosis can be formulated from the character of the cells obtained by the procedure.

EXPLANATION OF PLATE

Fig 1—Adult lymphocyte from lymph node. Red cells shown for magnification. Stained with Wright's stain, $\times 1,500$.

Fig 2—Reticular cell from a normal node. Note the few refractive granules in the cytoplasm. These are degenerative changes and were not present on first examination. In very fresh cells these granules are usually absent. Fresh preparation stained with neutral red and janus green, $\times 1,500$.

Fig 3—Immature cells from a lymph node of rapidly progressing lymphoblastoma in process of mitotic division. Wright's stain, $\times 1,500$.

Fig 4—Large reticulum cell with two nuclei, from a rapidly growing lymphoblastoma, lymphocyte nearby. Wright's stain, $\times 2,000$.

Fig 5—Three atypical early lymphoid cells in undifferentiated state from the lymph node of a rapidly growing lymphoblastoma. Wright's stain, $\times 1,500$.

Figs 6 and 7—Carcinoma cells from an adenocarcinoma of the cervical nodes. Wright's stain, $\times 1,500$.

Figs 8 and 9—Fresh carcinoma cells of cervical nodes. One of the cells shows two definite nuclei. Unstained, $\times 1,500$.

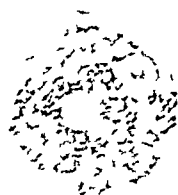
Fig 10—Cell removed from carcinomatous node three hours after roentgen-due to treatment. Fresh preparation stained with neutral red and janus green, $\times 1,500$.

Fig 11—Large degenerating cell taken from a rapidly growing lymphoblastoma. Wright's stain, $\times 2,000$.

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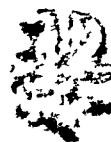
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11

INSULIN REACTIONS *

LEE FOSHAY, M.D.

George W. Crile Fellow in Research Medicine

CLEVELAND

A larger proportion of the recorded insulin reactions has occurred at a time when the analyses of the blood sugar have shown normal or elevated blood sugar concentrations. Many severe reactions have been observed at times when the blood sugar concentrations have been from 250 to 350 mg per hundred cubic centimeters of blood or even higher. These experiences have caused many observers to suspect that the fundamental cause of the so-called "hypoglycemic reaction" is not the hypoglycemia. Various explanations have been offered in an attempt to reconcile the severe reaction with a high blood sugar content. So far as I know, none of these has been free from serious criticism, and none has been a real explanation for every observed reaction, with the exception of the one offered here. This idea was first published two years ago.¹ Since that time, more evidence has been accumulated which seems to confirm the earlier work.

In May, 1925, Eadie, Macleod and Noble² showed that the injection of insulin into an animal caused a disappearance of glucose from fixed tissue cells. The importance of this fact in relation to insulin reactions has been either overlooked or underestimated. Two months later, I published results which demonstrated that insulin causes a similar disappearance of glucose from erythrocytes, and that insulin reactions appear only when the corpuscular glucose has fallen to around 45 mg per hundred cubic centimeters of blood.

The most severe reaction was noted at a time when the whole blood sugar was 300 mg and the corpuscular sugar 3 mg. Obviously this was not a hypoglycemia, because the blood sugar was about twice the value of what is commonly accepted as the upper normal limit. For want of a single descriptive term, I called this condition cytoglycopenia—a status of glucose impoverishment of the cells. The time relation of injections of insulin and reduced cellular glucose to the onset of symptoms of a reaction, both in the work of the Toronto investigators and in my own work, suggested that the reactions were caused by a lack of available

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1 Foshay, L. Observations Upon the Action of Insulin on the Blood with Special Reference to the Cause of the Condition Known as Hypoglycemia, *Am J Physiol* **73** 470 (July) 1925.

2 Eadie, G. S., Macleod, J. J. R., and Noble, E. C. Further Experiments on the Action of Insulin, *Am J Physiol* **72** 614 (May) 1925.

glucose within tissue cells, and that the corpuscular glucose concentration was a good index of the glucose concentration in the fixed tissues. All of these experiments were performed on animals. Eadie, Macleod and Noble worked with rabbits, while my work was done on dogs.

Since that time I have had the opportunity to observe a number of diabetic patients who were experiencing insulin reactions, and I have studied the distribution of glucose between plasma and erythrocytes before, during and after the appearance of the reactions. The results obtained are identical with those previously observed in the dogs.

Every insulin reaction is associated with a low corpuscular sugar. The sugar content of the whole blood or of the plasma bears no constant or direct relation to the reaction in regard to (1) the actual occurrence, even when of great severity, (2) the probability of occurrence, (3) the time of duration or (4) the severity. All combinations of these variables are possible with either a normal or a high blood sugar content. No insulin reactions have been observed without the coexistence of low corpuscular sugar. The immediate reactions, that is, those in which symptoms appear from one-half to two hours after the injection of insulin, are due to the same cause as the delayed reactions, wherein the symptoms and signs do not appear until six hours or longer after the injection. During the immediate reactions, there is a great disparity in the plasma and corpuscular sugars. The latter is always low, but the plasma or serum sugar is almost always high. During the delayed reactions the sugar falls gradually and usually with equal velocity in both the plasma and the corpuscles. The essential and common factor is the low corpuscular sugar.

Immediate reactions have been observed only under the following conditions: (1) in thin, undernourished patients, (2) in the presence of infections, (3) in coma, (4) after a single large dose of insulin and (5) after the last of a series of moderate sized, but often repeated, doses of insulin. Delayed reactions have occurred only when the patient has been well nourished, regardless of whether the dosage of insulin has been large or small, single or repeated. So far as my experience goes, the foregoing statements hold true for both children and adults.

What is the difference which permits of either an immediate or delayed reaction? Proof is difficult or impossible to obtain, but I think that the chief deciding factor is the presence or absence of an adequate storage of glycogen in the liver, perhaps also in the muscles. The nutritional state seems to be the only common factor possessed by the two groups of patients. All of the immediate reactions and almost all of the severe reactions have occurred in patients under conditions in which it has long been known that the stores of glycogen in the body are nearly exhausted. In these patients, when the sugar of the body is

depleted as a result of insulin, there is insufficient glycogenolysis to prevent the further reduction of tissue sugar to the level at which symptoms begin to appear, hence an early or immediate reaction. In the well nourished patient, even after a large dose of insulin, there is enough glycogen present in the body to furnish available glucose for a much longer period of time, so that if a reaction occurs at all it may come many hours after the dose of insulin.

As nearly as I can judge, the first symptoms of insulin reactions occurred in these patients at about the time when the cellular sugar was from 50 to 55 mg per hundred cubic centimeters of blood. During the height of the reaction the cellular sugar is usually lower, the lowest cellular sugar found was 20 mg. This patient had a severe infection and had been in uninterrupted coma for six days. As the transition from hyperglycemia to hypoglycemia and back to hyperglycemia was accomplished without return of consciousness, no symptoms could be obtained.

METHOD

The method of study employed is not difficult. The usual procedure was to take a sample of venous blood from an arm, taking care to prevent prolonged venous stasis. A sugar determination was made on the whole blood in the usual way. The blood may be either oxalated or defibrinated. The remainder of the blood was then centrifugalized at 1,500 revolutions a minute for fifteen minutes. The total volume and the volume of packed cells were read and the percentage of cells in the whole blood calculated. The supernatant serum or plasma was pipetted off and a sugar determination made on it. The corpuscular glucose was calculated from the foregoing data by the formula

$$\text{Cell sugar per cent} = \frac{\text{Whole blood sugar per cent} - (\text{serum sugar per cent by serum volume per cent})}{\text{Cell volume per cent}}$$

In this work, each sugar determination was made in quadruplicate by the method of Hagedorn and Jenson. A specimen of blood was drawn before the administration of insulin and usually at one hour and two hours after it had been administered. An attempt was made to get a specimen of blood at the onset of the reactions if any occurred.

This method of studying the effects of insulin on the distribution of glucose between plasma and erythrocytes in serial samples of blood from the same patient gives one a much more dynamic point of view of the utilization of carbohydrate in the patient than can be obtained by a study of the whole blood sugar alone. Moreover, it is possible by this method to predict with a remarkable degree of accuracy whether a patient will or will not have an insulin reaction after any given dose of insulin. In a well nourished patient it may not be possible to anticipate a delayed reaction, after a moderately large dose of insulin, but it is possible to predict all of the immediate reactions. A remarkably wide difference between the plasma and corpuscular sugar concentrations occurring two hours or less after the injection of insulin is always indicative of an impending reaction. The first three blood sugar values in the first case reported here demonstrate this well. I have been able to predict the occurrence or nonoccurrence of reactions correctly in about ten cases. All of the negative predictions are not included in this report (table 1).

Data Showing Insulin Reactions

Case	Patient	Date	Time	Insulin Units	Glucose Per Cent		Per Cent by Volume		Remarks
					Blood	Serum	Blood	Serum	
1	S B	12-20-25	2 55 p m	20	0 277	0 245	0 258	84.9	Patient in coma for six days
			3 00 p m		0 247	0 282	0 178	87.5	
			4 00 p m		0 197	0 220	0 036	87.5	Cytoglycopenia, reaction predicted
			5 00 p m		0 036	0 010	0 020	80.0	Hypoglycemia
			11 00 a m		0 261	0 200	0 121	79.5	Hypoglycemia
2	M O	12-22-25	11 00 a m	25	0 120	0 412	0 384	62.3	Before insulin and before breakfast
			1 19 26					37.7	Insulin and breakfast
			9 05 p m		0 224	0 213	0 185	67.2	No reaction predicted, none occurred
2	M O	1-26-26	11 15 a m	25	0 102	0 108	0 087	72.0	Severe reaction at 11 05 a m, four and one half hours after insulin
2	M O	1-11-26	6 25 i m	25	0 063	0 072	0 039	73.0	Reaction began at 10 25 a m, four hours after insulin
3	B J	1-21-26	7 30 a m	25	0 157	0 159	0 142	65.6	
			7 35 a m		0 132	0 131	0 133	59.0	No breakfast except black coffee
			9 30 a m		0 095	0 093	0 098	63.6	No reaction, it was so predicted
			10 30 a m		0 102	0 117	0 076	63.0	Same insulin and food as above
			7 35 a m		0 083	0 099	0 050	69.0	
3	B J	1-22-26	9 30 a m	25	0 086	0 089	0 063	64.0	Slow reaction predicted
			10 30 a m		0 095	0 097	0 091	63.0	Mild reaction at 11 25 a m
			11 30 a m		0 108	0 108	0 108	70.0	Suspected reaction at 1 00 p m
			3 00 p m					30.0	
			8 00 i m		0 119	0 115	0 127	68.0	
4	J S	1-29-26	10 00 a m	20	0 110	0 095	0 145	70.0	
			11 00 a m		0 083	0 093	0 060	70.0	
			11 30 a m		0 460	0 472	0 437	65.0	
			9 30 a m					35.0	
			10 30 a m					32.0	
5	Mc L	6-3-26	12 15 p m	10	0 259	0 270	0 239	64.3	
			12 20 p m		0 101	0 099	0 104	62.6	
			4 00 p m		0 253	0 284	0 204	69.9	
			9 00 a m					35.7	
								37.4	Slight reaction at 3 30 p m

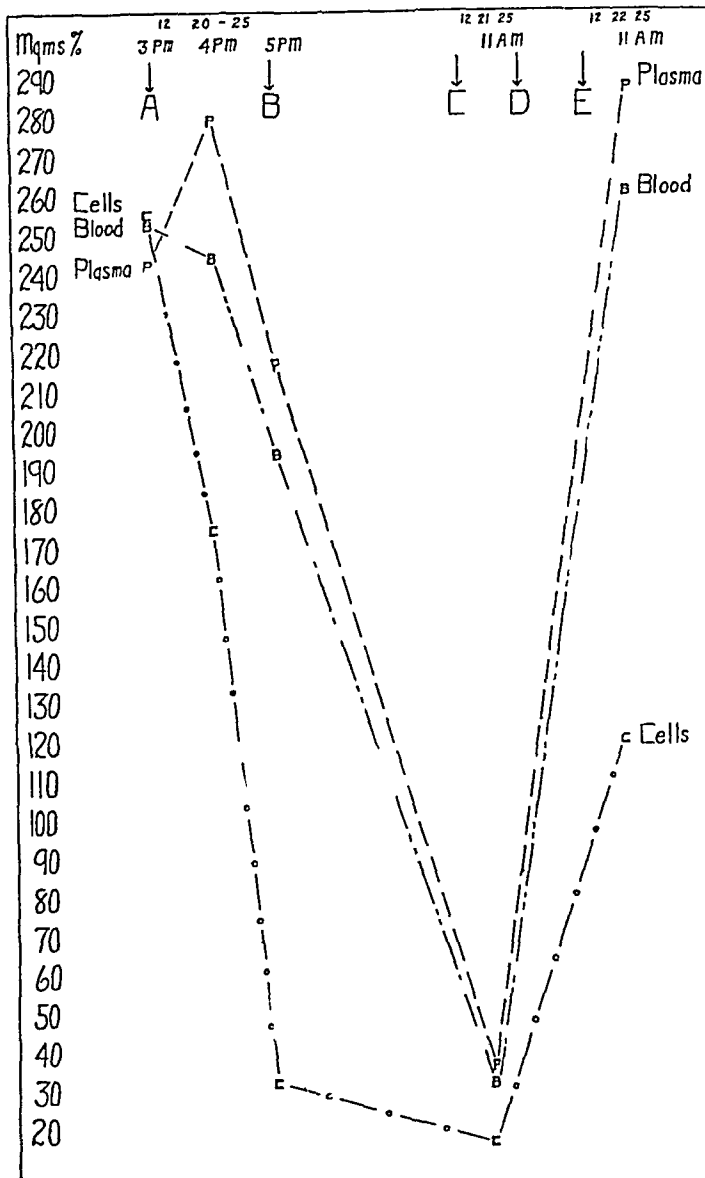
AUTHOR'S CASES

CASE 1—A colored woman, aged 42, had diabetes, tuberculous bronchopneumonia and osteomyelitis of the proximal phalanx of the third digit of the right hand, with gangrene of the entire finger. She had had the finger resected. She had been in coma for six days. On the day before the first sugar studies were made, the intern in charge had observed a strabismus of one eye. This had not been present before, and it caused him to suspect the presence of an insulin reaction. She had had only 20 units of insulin that morning. It was decided to repeat the same dose the next day to determine whether a reaction would occur and if its appearance could be predicted. The first specimen of blood was drawn at 3 p. m., and 20 units of insulin were immediately injected subcutaneously. One hour later, the corpuscular sugar was 0.178 per cent, two hours later, was 0.036 per cent, while the whole blood sugar was 0.197 per cent. I predicted that a severe reaction would soon follow and advised giving intravenous dextrose. This was not given, and the reaction occurred with strabismus as before. The patient received a transfusion of 500 cc of whole blood. The next morning, the blood sugar was 0.036 per cent and the corpuscular sugar 0.020 per cent, thus confirming the prediction of a real hypoglycemia. Dextrose was then given intravenously, and the results are shown in the final figures of this series. The changes are represented graphically in the chart.

CASE 2—A girl, aged 9, had severe diabetes and weighed 58 pounds (26.3 Kg.). She was receiving 25 units of insulin every morning and was having rather frequent mild insulin reactions, usually at about 11 a. m. On April 19, she received her customary 25 units of insulin. The first specimen of blood was drawn before either insulin or breakfast had been given. The second specimen, taken two and one quarter hours after the insulin, did not show cytglycopenia. It was predicted that there would be no reaction that day, none occurred. On April 26, she was observed at 11.05 a. m. with a moderately severe reaction. At that time, I made the following note: "lying quietly, pulse 120, normal cardiac mechanism, will not answer questions, frequently has short, jerky, clonic spasms which seem to pass like a rapid wave all over the body. No sweating, flushing or strabismus." The blood specimen was drawn at 11.25 a. m., a few minutes after recovery had begun. The sugar content was low, but within normal limits, in both plasma and cells. She had had 25 units of insulin at 8 a. m. In this instance, I was too late to record the cytglycopenia. However, on May 15, I observed the beginning of a moderately severe reaction. At 10.30 she was shaking all over, crying, complaining of hunger and had a pulse rate of 126. Blood was drawn immediately and showed a true hypoglycemia with a corpuscular sugar of 0.039 per cent. She had had 25 units of insulin at 6.30 a. m. followed at 6.45 by a breakfast which contained 30 Gm. of total available carbohydrate. The reaction came four hours after the injection of insulin. It was relieved in ten minutes by 50 cc of orange juice containing 5 Gm. of cane sugar.

CASE 3—A robust, young woman, white, in an excellent nutritional condition, had been having frequent symptoms of a mild insulin reaction for several weeks, usually late in the mornings. It had been her custom to take 25 units of insulin at 7.35 a. m., and to take only a cup of black coffee for breakfast. I brought her into the hospital for study and put her on the same routine which she had adopted at home. On the first day, two and three hour specimens of blood showed that the sugar values fell gradually and with equal velocity in both plasma and cells. After analysis of the two hour specimen of blood, it was predicted that a reaction would not occur, and none did occur. On the

next day the same experiment was repeated. The initial pre-insulin specimen of blood contained much less sugar than that of the previous day. The two hour specimen showed a low normal in the whole blood, 0.083 per cent and 0.050 per cent in the erythrocytes. A delayed reaction was predicted, and it occurred at 11 25, almost two hours after its approach had been recognized.



Curve showing severe hypoglycemia with recovery, *A* indicates the effect of 20 units of insulin administered subcutaneously, *B*, cytglycopenia without hypoglycemia, two hours after the administration of insulin (a severe insulin reaction was predicted and the administration of dextrose intravenously was advised), *C*, complete hypoglycemia (the patient had been given a blood transfusion but dextrose had not been given), *D*, dextrose given intravenously, *E*, recovery. The patient remained comatose throughout the entire period.

The remaining two cases are identical in a physiologic sense with case 3 and do not merit detailed description. Each of them represents the occurrence of a delayed reaction which was correctly predicted in both instances.

TREATMENT

Most of the patients with mild reactions do not require treatment. Usually the sensations of tremulousness, weakness, hunger and thirst pass away during the course of half an hour. The promptness with which symptoms disappear after the ingestion of food leads me to believe that glycogenolysis is the essential cause. I have seen a number of mild and moderately severe reactions dispelled within ten minutes by the ingestion of various foods, orange juice, orange juice with a small amount of cane sugar, cane sugar alone, mashed potato, a slice of bread, a glass of milk, in fact almost any kind of food. The relief of symptoms appears so rapidly that it cannot be accounted for by the digestion and absorption of the foodstuffs. It would seem that the presence of food in the stomach in some way causes a release of glycogen as glucose into the blood stream and thence into the tissues. If this is true, the injection of epinephrine should cause a prompt amelioration of symptoms. I have tried it a few times and have found it efficient. Of course, if the deposits of glycogen are practically exhausted, one could expect little improvement from the use of epinephrine. In such an instance, the vacuum for sugar would have to be met by the intravenous administration of dextrose.

CONCLUSIONS

The previous studies of insulin reactions have not been fruitful, because the only method of analysis has been a study of the whole blood sugar.

The occurrence of insulin reactions bears no direct fundamental relation to the whole blood sugar concentration.

The fundamental cause of the symptoms and signs of insulin reactions is believed to be a lack of available glucose throughout the tissue cells of the body.

The corpuscular glucose concentration may be accepted as an index of the glucose concentration in the cells of the fixed tissues.

A method is presented which enables one to anticipate the occurrence of many of these reactions hours before the first symptom appears.

Many impending reactions may be recognized early and completely prevented by proper prophylactic treatment.

This method is especially valuable for the study of patients who are in coma, for at that time the symptoms are lacking and the physical signs may be obscured.

THE PROBLEM OF THE IRON RESERVE*

AN EXPERIMENTAL STUDY

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AND

HAROLD N ETS, M S

CHICAGO

It is generally acknowledged that iron in the tissues, particularly in the liver and the spleen, acts as a reserve supply for the formation of hemoglobin, but definite experiments on changes in this iron reservoir are not readily available. In 1895, Kunkel¹ reported some work on puppies which were bled and then placed on an iron-poor and iron-rich diet. He found more iron in the tissue of the animals on the iron rich diet, but other dietary factors may have entered into his results.

In our previous work, we² have shown that ferric citrate given in the food and by subcutaneous injection does build up this iron reserve in the tissue, but that it has no effect on the rate of the formation of hemoglobin.

We have also noted that food iron is capable of being quickly and efficiently used in the formation of hemoglobin, an observation that is in agreement with the work of other investigators³. The next step was to determine to what extent, if any, food iron could be stored in the body in a utilizable form. While there is abundant evidence that food iron is readily utilized in the manufacture of hemoglobin, no satisfactory experiments are available to indicate whether or not the body may lay up a reserve supply of this food iron, thus having a certain amount on hand to use in case of a sudden demand for the formation of hemoglobin or whether the body lives from hand to mouth, taking in only such quantities as suffice for its daily needs.

*Read in abstract before the Association of American Physicians, Atlantic City, New Jersey, May 3, 1927.

*From the Department of Medicine, University of Illinois College of Medicine.

1 Kunkel, A. Pflüger's Arch **61** 595, 1895.

2 Williamson, C. S., and Ets, H. N. Value of Iron in Anemia, Arch Int Med **36** 333 (Sept) 1925.

3 Gibson, R. B., and Howard, C. P. Metabolic Studies in Pernicious Anemia, Arch Int Med **32** 1 (July) 1923. Rabschewitz-Robbins, F. S., and Whipple, G. W. Am J Physiol **79** 271, 1926. Murphy, W. P., Monroe, R. T., and Fitz, Reginald. Changes of Composition of Blood in Pernicious Anemia, J A M A **88** 1211 (April 16) 1927. Williamson, C. S. Influence of Age and Sex on Hemoglobin, Arch Int Med **18** 505 (Oct) 1916.

METHODS

When one group of six dogs was placed on a diet consisting of bread and milk and another group on a diet in which part of the bread and milk was replaced by beef spleen, we have noted that, although all the dogs maintained a normal concentration of hemoglobin, the dogs on the diet containing beef spleen had nearly twice as much iron in their livers and spleens as the dogs on the diet consisting of bread and milk.

To begin with, six normal dogs were killed and then livers and spleens analyzed with the result that the average iron content of the liver was found to be 27.3 mg and that of the spleen 118.6 mg per hundred grams of tissue.

The concentration of hemoglobin of six healthy dogs was determined, and then the animals were placed on a diet containing, in addition to

TABLE 1—*Observations of Dogs on Beef Spleen Diet*

Dog	Hemoglobin Concentration			Iron Analyses	
	7/10/25	10/7/25	12/11/25	Liver	Spleen
1	1.228	1.193	1.330	55.4 mg	179.5 mg
2	1.200	1.026	*	90.0 mg	280 mg
3	1.319	1.280	1.326	52.0 mg	130 mg
4	1.305	1.034	*	69.6 mg	416 mg
5	1.248	1.197	*	41.2 mg	412 mg
6	1.248	1.239	1.330	53.5 mg	400 mg
Average	1.258	1.162	1.329	60.3 mg	302.9 mg

* Killed on Oct. 7, 1925

TABLE 2—*Changes in Average Iron Content in Livers and Spleens*

	Livers	Spleens
Normal dogs	27.3 mg	118.6 mg
Dogs after about four months' spleen feeding	60.3 mg	302.9 mg

bread and milk, beef spleen in considerable amounts. Table 1 shows the results.

As is evident from table 2, the average iron content of the livers rose from 27.3 to 60.3 mg, and that of the spleens from 118.6 to 302.9 mg.

This experiment shows merely that animals on bread and milk plus beef spleen store up more iron in their livers and spleens than animals on bread and milk only.

In this experiment, only a small number of animals was used and no demand was made for the formation of hemoglobin. In order to investigate further the iron supply of the tissue, the following experiments were devised.

A large number of young rats was obtained and divided into two groups. To insure uniformity, the litters were divided, so that half of the young were in each group. One group was placed on the standard casein diet which was slightly modified so that its caloric and protein content was comparable to the

TABLE 3—Hemoglobin Concentrations Expressed as Extinction Coefficients

Liver Diet				Casein Diet			
Rat	May 21	July 1	September 25	Rat	May 21	July 1	September 25
200	0.795	1.203	1.177	201	0.853	1.076	1.233
203	0.849	1.180	1.109	202	0.872	1.166	1.068
204	0.851	1.091	1.025	208	0.836	0.845	0.970
206	0.887	0.927	1.251	209	0.907	1.098	1.180
207	0.870	1.203	1.256	210	0.849	0.949	1.185
215	0.860	1.166	1.180	211	0.915	1.180	1.008
220	0.866	0.990	1.163	212	0.893	1.098	1.185
224	0.831	0.981	1.020	217	0.849	1.157	1.277
228	0.911	1.185	1.018	218	0.872	0.797	0.741
230	0.872	1.180	1.144	219	0.830	1.114	1.068
231	0.820	1.044	1.066	221	0.905	1.063	1.203
233	0.986	0.940	1.049	222	0.575	1.119	1.049
235	0.778	1.177	1.233	223	0.809	1.135	1.251
238	1.022	1.119	1.215	225	1.006	1.029	0.788
243	0.864	1.155	0.997	227	0.729	0.934	1.076
247	0.778	0.879	1.168	229	0.931	1.185	1.157
248	0.698	1.091	1.099	232	1.083	0.942	1.127
249	0.806	1.034	1.221	234	0.843	1.078	1.163
250	0.747	1.056	1.032	237	0.807	1.083	1.015
251	0.936	1.215	1.248	239	0.887	1.044	0.963
255	0.864	1.037	1.025	241	0.947	1.015	0.845
257	0.919	1.168	1.191	242	0.804	0.748	0.970
259	0.895	1.034	1.037	244	0.748	1.146	1.220
260	0.957	1.093	1.168	245	0.737	1.053	0.823
263	0.823	1.149	1.099	246	0.883	0.999	1.368
264	0.834	1.146	1.053	252	0.911	1.114	1.197
266	0.840	1.044	1.119	253	0.962	0.990	1.163
269	0.862	1.166	1.068	254	0.889	1.119	1.044
270	0.735	1.083	0.931	256	0.913	1.135	1.263
272	0.816	1.157	1.101	258	0.759	1.046	0.716
273	0.707	1.283	1.146	261	0.758	1.059	1.119
274	0.788	1.101	1.109	262	0.823	0.944	1.171
275	0.800	1.101	1.094	265	0.883	1.146	1.157
277	0.845	1.098	1.157	267	0.853	0.949	0.737
278	0.911	0.874	1.180	276	0.741	1.088	1.119
279	0.855	1.083	1.203	282	0.795	0.845	1.039
281	0.763	1.166	1.006	292	0.807	1.109	1.306
283	1.022	1.127	1.160	294	0.799	1.068	1.125
290	0.768	1.093	1.261	295	0.781	0.781	0.975
292	0.813	1.133	1.209	296	0.774	1.073	1.209
297	0.786	1.106	1.203	311	0.671	1.066	1.125
298	0.895	1.103	1.025	312	0.732	1.041	1.270
299	0.816	1.078	1.194	313	0.664	0.917	1.004
301	0.698	1.130	1.088	315	0.583	1.029	1.008
302	0.659	1.068	1.025	316	0.580	0.915	1.022
304	0.724	1.032	1.125	317	0.602	1.046	1.313
305	0.572	1.081	1.011	318	0.687	0.929	1.006
306	0.674	1.119	1.091	320	0.636	1.073	1.212
308	0.615	1.191	1.051	322	0.627	1.029	1.034
309	0.538	1.063	1.114	323	0.698	1.155	1.188
310	0.555	1.051	1.010	324	0.638	0.977	1.174
314	0.661	1.066	1.049	326	0.677	1.155	1.251
319	0.651	1.049	1.215	327	0.716	1.223	1.174
321	0.671	1.032	1.037	328	0.704	0.999	1.163
325	0.713	1.051	1.088	332	0.559	1.049	0.831
329	0.768	1.049	0.949	333	0.612	1.020	0.816
330	0.588	1.051	1.044	336	0.547	1.093	1.203
331	0.745	1.130	1.099	338	0.510	0.929	1.082
334	0.536	1.163	1.133	340	0.548	0.901	1.277
335	0.494	1.061	1.088	342	0.521	0.912	1.039
337	0.578	1.152	1.091	344	0.656	0.995	1.053
339	0.521	1.096	1.071	345	0.536	1.194	1.058
341	0.567	0.938	1.033				
343	0.497	1.119	1.141				
Average	0.770	1.092	1.110	Average	0.766	1.035	1.091

experimental diet This experimental diet was based on the standard casein diet, but derived its protein from dried beef liver (instead of casein) Both these diets were adequate in all respects, as we observed from charts showing the growth curve and from the successful rearing of the young

The hemoglobin was determined on these rats just before they were placed on the diets, and then at intermediate times after they had been on the diets up to four months

TABLE 4—Iron Content of Organs Before Bleeding

	Casein Diet	Liver Diet
Livers	14.2 mg	22.2 mg
Spleen	21.3 mg	31.2 mg

TABLE 5—Results of Determinations of Hemoglobin After Bleeding

Original Liver Diet Group					Original Casein Diet Group				
Rat	Before Bleeding Sept 25	Six Days After Bleeding	Fourteen Days After	Twenty Eight Days After	Rat	Before Bleeding Sept 25	Six Days After Bleeding	Fourteen Days After	Twenty Eight Days After
200	1.177	0.923	0.893	0.809	209	1.180	0.936	0.975	0.957
203	1.109	0.800	0.919	0.866	211	1.008	0.759	0.834	0.917
204	1.025	0.903	0.913	0.843	218	0.741	0.580	0.610	0.487
206	1.261	1.197	1.181	1.114	219	1.068	0.792	0.644	0.735
215	1.180	0.786	0.947	1.073	221	1.203	0.667	0.591	0.407
220	1.163	0.907	1.004	1.004	223	1.251	0.689	0.792	0.831
228	1.018	0.995	1.068	1.076	225	0.788	0.816	0.648	0.599
230	1.144	0.999	0.911	0.919	227	1.076	0.707	0.723	0.553
231	1.066	0.919	1.083	1.111	229	1.157	0.745	0.632	0.697
238	1.215	0.934	0.866	0.856	232	1.127	0.671	0.855	0.960
247	1.168	1.034	1.135	1.144	234	1.163	0.836	0.829	0.696
249	1.221	0.983	0.907	0.954	239	0.968	0.702	0.671	0.740
250	1.032	0.827	1.046	1.133	241	0.845	0.507	0.618	0.583
251	1.248	0.966	0.981	1.146	242	0.970	0.885	0.823	0.733
255	1.025	0.940	1.114	1.071	244	1.220	0.944	0.825	0.919
257	1.191	1.058	0.880	0.891	245	0.823	0.947	0.881	0.753
259	1.037	0.983	1.020	1.029	246	1.368	0.807	0.640	0.533
260	1.168	0.834	1.004	1.027	254	1.044	0.768	0.679	0.718
264	1.053	0.835	1.029	0.607	256	1.236	0.823	0.674	0.615
266	1.119	0.992	1.144	1.011	262	1.171	0.671	0.610	0.654
269	1.068	0.915	1.039	1.001	265	1.157	0.738	0.662	0.542
272	1.101	0.823	0.934	1.041	267	0.737	0.629	0.792	0.575
273	1.146	1.039	1.227	1.293	282	1.039	0.578	0.698	0.831
274	1.109	0.915	1.013	0.955	292	1.306	0.735	0.949	1.058
275	1.094	0.988	1.068	1.103	294	1.125	0.905	0.979	0.942
277	1.157	0.940	1.083	1.053	296	1.209	0.988	0.813	0.690
279	1.203	0.979	1.114	1.103	312	1.270	0.630	0.755	0.769
281	1.066	0.940	1.011	0.858	315	1.125	0.779	0.681	0.626
290	1.261	0.953	1.058	1.033	317	1.313	0.907	0.887	0.887
298	1.025	1.020	1.046	0.761	322	1.034	0.489	0.611	0.774
299	1.194	1.116	1.290	1.209	323	1.118	0.741	0.825	0.876
301	1.088	0.997	1.029	1.068	327	1.174	0.610	0.647	0.692
302	1.025	1.041	1.056	1.133	328	1.163	0.642	0.523	0.548
305	1.011	1.015	0.799	1.037	333	0.816	0.814	0.813	0.702
306	1.091	0.942	1.058	1.152	336	1.203	0.795	0.690	0.962
308	1.051	0.925	1.034	1.197	338	1.082	0.671	0.582	0.692
309	1.114	0.813	1.106	0.953	340	1.277	0.683	0.712	0.759
310	1.010	0.755	0.781	0.981	342	1.049	0.665	0.768	0.719
314	1.049	1.015	0.979	0.936	344	1.125	0.800	0.577	0.975
321	1.037	0.780	0.827	0.862	345	1.058	0.683	0.732	0.799
325	1.088	0.732	0.764	0.983					
329	0.949	0.698	0.845	0.981	Average	1.096	0.715	0.752	0.735
330	1.044	0.919	1.017	1.303					
331	1.099	0.916	0.990	1.188					
335	1.088	0.797	0.953	1.098					
337	1.091	0.755	0.899	0.972					
339	1.071	0.880	0.905	0.940					
341	1.133	1.037	0.921	1.073					
343	1.141	0.944	1.122	1.283					
Average	1.104	0.927	1.005	1.093					

Twenty of the animals were then killed, and determinations of the iron made on their livers and spleens

The remaining rats were next bled 25 per cent of their blood volume, and then both groups were placed on the original standard casein diet. Determinations of the hemoglobin were then made on the sixth, fourteenth and twenty-eighth days after bleeding, and the results are recorded in table 5

At this time, twenty-eight days after bleeding, another twenty rats from each group were killed, and determinations of the iron made on their livers and spleens

The rats that had been on the modified casein diet during the prebleeding period were placed on the liver diet about fifty days after bleeding, and determinations of the hemoglobin were made just before they were placed on the new diet, and after they had been on the diet for twenty-four days

These animals were then killed and determinations of the iron were made on their livers and spleens

The determinations of hemoglobin were made by the spectrophotometric method, as given in a previous publication⁴ This method is of great value

TABLE 6—*Iron Content of Organs of Rats Twenty-Eight Days After Bleeding*

	Casein Diet	Liver Diet
Liver	9.9 mg	13.3 mg
Spleen	14.1 mg	29.5 mg

TABLE 7—*Determinations of the Iron in Rats Before and After Being Placed on Liver Diet*

Rat	Before Being Placed on Liver Diet, Hemoglobin Concentration	After Twenty Four Days on Liver Diet, Hemoglobin Concentration
—322	0.832	1.127
—225	0.678	1.144
—223	0.735	1.068
317	0.806	0.818
262	0.781	1.091
342	0.823	1.127
328	1.046	1.125
336	0.751	1.032
327	0.959	1.168
335	0.751	1.163
265	0.578	1.197
315	0.686	1.025
239	0.732	1.125
311	0.860	1.126
232	0.692	1.071
Average	0.780	1.093

because of the small amount of blood required, the high degree of accuracy attained, since there are no standards to deteriorate, and, as in this case, in which only comparative values are wanted, its independence of errors in calibration. The values given in the tables are the average of four readings, and are expressed in terms of extinction coefficients, a factor which varies directly with the concentration of hemoglobin. The determinations of iron were made by the method of Ripper-Schwarzer.

RESULTS

Table 1 shows that the concentration of hemoglobin of the dogs on the two diets is about the same, and table 2 shows that the dogs on the diet containing beef spleen have much more iron in their livers and spleens than the dogs on the bread and milk diet.

⁴ Williamson, C. S. Influence of Age and Sex on Hemoglobin, Arch. Int. Med. 18:505 (Oct.) 1916.

The experiments with rats show that the concentration of hemoglobin was approximately the same in both groups of animals in the prebleeding period (table 3). However, the iron content of the liver and spleen is much higher in the animals on the liver diet than in the animals on the casein diet (table 4).

The rate of regeneration of hemoglobin is different in the two groups of rats after bleeding. The rats that were on the modified casein diet show no regeneration of hemoglobin, while those on the liver diet show a gradual regeneration, coming back nearly to normal in twenty-

TABLE 8—*Determinations of Iron in Liver and Spleen*

	Casein Diet (Before Liver Feeding)	Casein Diet (After Liver Feeding)
Liver	9.9 mg	14.6 mg
Spleen	14.1 mg	23.8 mg

TABLE 9—*Summary of Investigation*

Before Bleeding	Liver Diet	Casein Diet
Hemoglobin concentration	0.770	0.766
Mg of iron per 100 Gm liver	22.2	14.2
Mg of iron per 100 Gm spleen	51.2	21.3
After Bleeding (Changed to Standard Casein Diet)		
6 days after bleeding, hemoglobin concentration	0.927	0.745
14 days after bleeding, hemoglobin concentration	1.005	0.732
28 days after bleeding, hemoglobin concentration	1.033	0.735
Mg of iron per 100 Gm liver	13.3	9.9
Mg of iron per 100 Gm spleen	29.5	11.1
Loss, mg of iron per 100 Gm liver	8.9	4.3
Loss, mg of iron per 100 Gm spleen	21.7	7.2
Change of Group on Casein Diet to Liver Diet		
Hemoglobin concentration at beginning	0.780	
Hemoglobin concentration twenty four days later	1.093	
Mg of iron per 100 Gm liver	14.6	
Mg of iron per 100 Gm spleen	53.8	

eight days. Most of this regeneration occurred in the first six days, demonstrating that the stored up reserve iron is, in a form, capable of being rapidly utilized (table 5).

A comparison of tables 4 and 6 shows that, after bleeding, the livers of the group on the liver diet gave up more than twice as much iron as the livers of the group on the casein diet, while the spleens in the former group gave up three times as much iron as the spleens of the latter group.

In table 7 it is seen that the rats on the modified casein diet, which showed no regeneration of hemoglobin after bleeding, gradually came back when they were placed on the liver diet, and table 8 shows that the iron in their livers and spleens had also returned to normal figures.

COMMENT

This investigation may be divided into three parts For convenience, we have summarized our results in table 9

In the first part of the investigation, in which the animals were on the two different diets, storage of iron was made in the tissues of the group on the liver diet, as is evident from a comparison of the amount of iron in the liver and spleen of the two groups of animals, there being 141 per cent more iron in the spleens and 57 per cent more iron in the livers of the rats on the liver diet than in those on the casein diet The concentration of hemoglobin remained about the same, since there was enough iron in the casein diet to replace the normal amount of destruction of hemoglobin

In the second part of the investigation, the animals were placed on the same diet so that any differences which resulted from the strain placed on their hemoglobin forming function would be due to their previous treatment After bleeding, the rats which were on the casein diet during the first period showed practically no regeneration of hemoglobin However, the rats which had been on the liver diet during the pre-bleeding period showed entirely different results Even as early as the sixth day after bleeding, their hemoglobin was 20 per cent above that of the group on the casein diet, and on the fourteenth and twenty-eighth days this regeneration was much more marked On the latter date, the rats on the liver diet were back nearly to normal

Looking at the results of the determinations of iron in another way, we may say that the livers of the group on the liver diet gave up 8.9 mg of iron per hundred grams of organ, as compared to 4.3 mg in the group on the casein diet In the same way, the spleens of the group on the liver diet gave up 21.7 mg per hundred grams of organ weight as compared with 7.2 mg in the casein group Since the weight of the liver averages about eight times that of the spleen, it will be seen that the liver is the more important factor Further inspection of table 9 shows that the livers in the group on the liver diet, even at the end of the experiment, contained about one-third more iron than the livers of the group on the casein diet, so that this fact will make it probable that there was still more iron in these livers capable of being utilized in the formation of hemoglobin if the experiment had been continued sufficiently long

The difference in the recovery of the two groups after bleeding can be interpreted only as the result of the building up of a reservoir of utilizable iron in the tissues, which can be readily transformed into hemoglobin when a strain is placed on the hemopoietic organs Although the rats on the liver diet did not regenerate their hemoglobin to the full pre-bleeding figure, yet the results are decisive and clear cut It is of course possible, perhaps even probable, that a longer continued period

of observation would have shown a complete recovery, and that a longer period of liver feeding might have resulted in a still greater storage of iron, so that our figures must be interpreted as applying only to our conditions of experiment

In the third part of the experiment, the rats on the casein diet which had been on the standard casein diet for fifty days after bleeding and which had shown practically no tendency to regenerate hemoglobin were placed on the liver diet. After only twenty-four days, these rats had regenerated sufficient hemoglobin to bring their concentration of hemoglobin back to normal, and at the same time to deposit 4.7 mg of iron in their livers, and 9.7 mg of iron in their spleen, both reckoned per hundred grams of tissue, this deposit of iron bringing the organs back again to practically normal figures

This part of the experiment indicates clearly that even when the animals have no reserve of iron in their tissues they will still manufacture hemoglobin from their food, if it is sufficiently rich in iron, and will also deposit iron in significant quantities in their livers and spleens

CONCLUSIONS

1 A reservoir of readily utilizable iron can be built up in the livers and spleens of rats by placing them on a diet containing liver

2 This stored iron is capable of being used in the regeneration of hemoglobin after the production of an anemia by bleeding

3 Rats rendered anemic by bleeding, the iron reserve of which has been exhausted, recover their concentration of hemoglobin rapidly on being placed on a diet containing liver, and simultaneously build up a reserve of iron in their livers and spleens

DIABETES MELLITUS

REPORT OF A CASE REFRACTORY TO INSULIN¹

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One of the striking features of the insulin treatment for diabetes mellitus is the uniformity with which even the most severe forms respond to the injections of insulin. From time to time, however, cases have been reported that seem relatively refractory to insulin. Some of them are more refractory than others, but none of them compare, in this respect, with a case we recently observed.

Charlton¹ reported a patient with severe diabetes who, on a restricted diet, did not respond to 102 units of insulin. The patient was syphilitic, and after a course of antisyphilitic treatment responded readily to injections of insulin.

Mahler and Pasterny² reported a case of diabetes mellitus in which a hypophysial tumor was present. Sixty units of insulin produced practically no effect on blood sugar or glycosuria but did produce a marked hydremia.

Charles and Clarac³ observed a case of diabetes showing a blood sugar of 326 mg per cent and a daily output of 250 Gm of sugar, marked acidosis was present. The daily injection of 60 units of French insulin modified neither the hyperglycemia, the glycosuria nor the ketonuria. The patient nevertheless improved and gained 8 Kg.

A case that aroused much interest in Viennese medical circles was reported about three years ago from Falta's clinic⁴. An obese young man presented a typical severe diabetes, with acidosis. A rigid diet reduced the hyperglycemia and the glycosuria a little, but practically no effect could be noted from injections of insulin up to 160 units daily. Even when the patient was placed on a fasting diet, 20 units of

* From the Medical Service of the Jewish Hospital of St Louis

1 Charlton, P H. Diabetes Refractory to Insulin Relieved by Anti-syphilitic Treatment, *Endocrinology* 8 235 (March) 1924

2 Mahler, P, and Pasterny, K. Clinical Observations on Insulin Action in Diabetes Mellitus, *Med Klin* 20 337 (March 16) 1924

3 Charles and Clarac. Two Cases of Diabetes Treated with Insulin, *J de med de Bordeaux* 102 384 (May 10) 1925

4 Falta W. On an Insulin Refractory Case of Diabetes Mellitus, *Klin Wchnschr* 3 1315 (July) 1924. Radoslav, C S. The Action of Insulin on the Blood Sugar of Man, *Wien Arch f inn Med* 8 395 (July) 1924

insulin given subcutaneously did not produce any effect on the blood sugar and, when it was given intravenously, the effect was minimal and of brief duration

In his discussion of the case, Falta suggested that this patient may not have had a pancreatic diabetes at all but that, with a normal production of insulin on the part of the organism, the disturbance may have been elsewhere. Three months later, Bosch⁵ recorded the further progress of the patient. He had been taken off insulin and put on a rigid Petren diet, consisting exclusively of 5 per cent vegetables with from 200 to 250 Gm of fat. The daily output of sugar in the urine fell from 30.4 to 1.5 Gm; occasionally, the urine was free from sugar. The blood sugar fell to 0.16 per cent, and the patient was subjectively improved.

A similar case was recently reported by Kaufmann,⁶ briefly and without detail, incidentally to a discussion of methods of determination of

TABLE 1—*Blood Sugar in Mg Per Cent in Falta's Case*

Twenty Units Injected	Blood Sugar Before Injection	Blood Sugar After Injection				
		1 Hr	2 Hrs	3 Hrs	4 Hrs	5 Hrs
Subcutaneously	252	255	258	261	256	252
Intravenously	250	148	251	268	303	

TABLE 2—*Kaufmann's Case*

Units of insulin injected	20	30	50	100	100
Blood sugar before injection	322	375	324	293	274
Blood sugar one hour after injection		348	341	280	204
Blood sugar two hours after injection	322	316	255	213	154

blood sugar. Table 2 illustrates this patient's lack of response to moderate doses of insulin and her relatively slight response to large doses. The insulin was injected subcutaneously while the patient was fasting, the blood sugar is in mg per cent.

Other cases of diabetes mellitus more or less refractory to insulin have been reported, usually without much detail, by Matthes,⁷ von Noorden and Isaac,⁸ Jaksch-Wartenhorst,⁹ Strauss,¹⁰ Umber and

5 Bosch, E. On an Insulin Refractory Case of Diabetes Mellitus, *Klin Wchnschr* **3** 1861 (Oct) 1924

6 Kaufmann, E. Rapid Micro-Determination of Blood Sugar, *Med Klin* **22** 1219 (Aug 6) 1926

7 Matthes. Concerning Insulin, *Deutsche med Wchnschr* **50** 487 (April 18) 1924

8 Von Noorden, C, and Isaac, S. Further Experiences Concerning Insulin Treatment of Diabetes, *Klin Wchnschr* **3** 720 (April 22) 1924

9 Jaksch-Wartenhorst, R. Insulin and Diabetes, *Zentralbl f inn Med* **45** 2 (Jan 12) 1924

10 Strauss, H. Concerning Insulin-Resistant Diabetes, *Klin Wchnschr* **4** 491 (March 12) 1925

Rosenberg¹¹ and Keller¹² In some but not all of the patients, the diabetes was complicated by dysfunction of the thyroid and pituitary glands None of them were even approximately as refractory to insulin as the following case recently observed in the medical service of the Jewish Hospital of St Louis

REPORT OF CASE

M W, a young unmarried woman, had never been ill until late in 1922 Then thirst and polyuria with progressive loss of weight and strength set in, and when first seen in March, 1923, she was found to have a mild diabetes She was easily made sugar free and on a diet consisting of protein, 75, fat, 110, carbohydrate, 75, remained so for more than two years She then became careless about her diet and when she returned in December, 1925, was found to have a more obstinate glycosuria with a fasting blood sugar of 198 mg per cent She spent ten days in the Jewish Hospital and was discharged, sugar free, on a diet of protein, 54, fat, 120, and carbohydrate, 84, with 8 units of insulin twice daily

She was readmitted four weeks later, on account of sensitization to insulin in a somewhat unusual form From five to seven hours after the administration of insulin, a large area of induration appeared at the site of injection, reaching a diameter of 10 cm in from twelve to fifteen hours, the area was hot, angry and tender for twelve hours more and then gradually faded The reaction was identical with several brands of insulin The addition of epinephrine to the insulin or its subsequent injection into the indurated area did not alter the reaction The lower down in the body the injections were made, the more violent was the reaction, the latter always remained strictly confined to the site of the injection, there was no urticaria, angioneurotic edema or asthma The reactions were just as severe with beef insulin as with the usual pork insulin, and were therefore to be ascribed to the insulin itself, not to the protein contamination The patient was urged to continue the use of insulin in spite of the discomfort and gradually desensitization took place, the reactions ceased to occur

For several months the patient remained sugar free on protein, 54, fat, 120 and carbohydrate, 110, with 30 units of insulin twice daily In June, 1926, however, it was found necessary to reduce the carbohydrate to 60 Gm and to increase the daily dose of insulin to 70 units She then remained sugar free until September 1, when she found herself unable to control the glycosuria, in spite of an increase in the insulin dosage to 150 units daily

She was readmitted to the Jewish Hospital, Sept 10, 1926, with considerable glycosuria and acidosis and a fasting blood sugar of 362 mg per cent She was put on a diet consisting of protein, 30, fat, 120 and carbohydrate, 30, with 60 units of insulin The excess of fat was evidently an error, for she promptly went into coma, accompanied by restlessness, semiconsciousness and a rapid, thready pulse, the urine contained much sugar, diacetic acid, albumin and casts Under a regimen consisting of large doses of insulin with glucose given intravenously, digifolin and hypodermoclysis, recovery was prompt Thereafter, the fat in the diet was kept low, but in spite of large doses of insulin it was not

¹¹ Umber F and Rosenberg, M Concerning Insulin Refractory Glycosurias, *Klin Wchnschr* 4 583 (March 26) 1925

¹² Keller, F A Case of Diabetes Mellitus Refractory to Insulin, *Wien klin Wchnschr* 39 1396 (Nov 25) 1926

found possible to keep the patient sugar free for more than an hour or two at a time. It is interesting to note that occasionally, after large doses of insulin, she still had an urticarial reaction but that this was now generalized instead of being confined to the site of injection, as had occurred at first.

Her lack of response to insulin at this time is well illustrated in table 3. On three successive days the patient received 50, 200 and 300 units of insulin, intravenously, she was fasting and was not receiving any food during the progress of the experiment.

The blood sugar was determined by the Shaffer-Hartmann micromethod,¹³ 0.1 or 0.2 cc of blood, allowed to flow freely from the finger tip or the lobe of the ear, was used for each determination. It is clear from the table that 50 units

TABLE 3—*Influence on the Blood Sugar of Insulin Injected Intravenously While the Patient was Fasting*

	Blood Sugar in Mg Per Cent				
	Insulin 50 Units			Insulin 200 Units	Insulin 300 Units
	Sept 14	Sept 15	Oct 5	Sept 15	Sept 16
Before injection	580	508	412	533	300
One half hour after injection	570	724	308	500	282
One hour after injection	545	788	276	434	240
Two hours after injection			239	376	148
Three hours after injection	532	533	252		82
Four hours after injection					156
Maximum fall in blood sugar	48	0	173	177	218
Average urine in sugar in Gm per hour		7		8	0.3

TABLE 4—*Comparative Effect on the Blood Sugar of 50 Units of Insulin Given to the Fasting Patient Intravenously and Subcutaneously*

	Blood Sugar in Mg Per Cent				
	Before Injection	Time After Injection			
		½ Hr	1 Hr	2 Hrs	3 Hrs
Subcutaneous injection	298	334	316	304	296
Intravenous injection	500	534	533		139
					Total Fall of Blood Sugar
					2
					61

of insulin did not produce any effect on the blood sugar, 200 units a slight effect, while even the enormous dose of 300 units did not result in any hypoglycemia and required three hours to reduce the blood sugar to the normal level. During these four days, the patient showed only a slight acidosis and felt well.

As it had been suggested that insulin might be more effective when given subcutaneously than when given intravenously, the former method was also tried. Each of three days was begun by injecting 50 units subcutaneously and following the blood sugar through three hours before giving any food. Table 4 shows the comparative effect of 50 units given intravenously and subcutaneously. Each series is the average of three such tests.

The comparison in table 4 is perhaps not fair, as the subcutaneous doses happened to be given while the blood sugar level was lower than when the intravenous doses were given. The greater effectiveness of the intravenous method is clear, however.

In an attempt to increase the response of the patient to insulin, it seemed worth while to try the effect of parathyroid extract. Winter and Smith,¹⁴ in 1923, had shown that when insulin and parathyroid extract were injected simultaneously into fasting rabbits, hypoglycemic convulsions ensued in a much shorter period than after plain insulin and with only from one third to one fourth of the usual dose of the latter. Forrest¹⁵ even published reports of the blood sugar curves of five diabetic patients who, while fasting, received insulin subcutaneously and parathyroid tablets by mouth. The average fall in the blood sugar when 15 or 20 units of insulin alone was given was 163 mg per cent, after the administration of insulin plus from 4 to 12 parathyroid tablets, it was 239 mg per cent, nearly half as much again. Cammidge and Howard¹⁶ found that the hydrolysis of sugar by liver extract in vitro is retarded by insulin, and that this retardation is greatly increased when parathyroid extract is also added. In our patient, parathyroid extract did not seem to be without effect. On successive days, she was given 50 units of insulin subcutaneously, with the addition of increasing amounts of parathyroid extract. She had fasted more than twelve hours before the injection, and did not receive any food during the period of observation.

TABLE 5—*Effect on Blood Sugar of Injecting 50 Units of Insulin Hypodermically, While Patient was Fasting, Together with Varying Amounts of Parathyroid Hormone*

	50 Units Insulin Plus Parathyroid Extract			
	None Mg Per Cent	1 Cc Mg Per Cent	2 Cc Mg Per Cent	3 Cc Mg Per Cent
Before injection	314	364	318	289
One half hour after injection	316	314	378	283
One hour after injection	315	297	354	259
Two hours after injection	280	292	314	227
Three hours after injection	281	284	271	169
Maximum fall in blood sugar	36	80	102	120

An instructive example of the patient's behavior toward insulin is seen in the blood sugar during and after a day of profound acidosis. On October 15, an attempt was made to see how the patient would react to a low calory diet without insulin. On that day she was given a total of protein, 15, fat, 18 and carbohydrate 32 (357 calories) divided into three meals. The following morning she was found in a precomatose state with the usual symptoms. During that day, she received 900 units of insulin, which did not produce any perceptible effect on the blood sugar, and it was not until the next day, when an additional 265 units of insulin was given, that the condition of profound acidosis cleared up. On the third day, however, before any more insulin had been given—indeed fifteen hours after the last dose—the fasting blood sugar was only 60 mg per cent. It remained low all that day, and there was a little sweating suggestive of hypoglycemia. On the fourth day, the fasting blood sugar was only 58 mg per cent, at noon, it rose to 390 mg per cent and remained high thereafter.

14 Winter, L. B., and Smith, W. Possible Relation Between Pancreas and Parathyroids, *J. Physiol.* 58 108 (Oct.) 1923.

15 Forrest, W. D. The Effect of Parathyroid on the Blood Sugar Curve After Insulin, *Brit. M. J.* 2 916 (Nov. 17) 1923.

16 Cammidge, P. J., and Howard, H. A. H. Influence of Insulin upon the Activity of the Diastatic Ferment of the Liver, *J. Metabol. Res.* 5 95 (Jan., Feb.-March) 1924.

This observation indicates clearly that, in this patient at least, the insulin is not rapidly excreted, as is generally supposed, but must have circulated in the blood, unaltered for many hours. It is also in harmony with the hypothesis that, in this case, the hyperglycemia was due to the lack of some associated glycolytic ferment. If the latter is supposed to have been absent, or nearly so, during the first two days, and then to have been produced again in a more nearly adequate amount, the drop in blood sugar can be readily explained.

The response of the patient to insulin varied greatly from day to day but was always less than in cases of ordinary diabetes. The total carbohydrate utilized per unit of insulin injected rarely rose above 0.7 Gm, sometimes fell below 0.3 Gm and averaged 0.53 Gm. On the whole, as is usually the case in diabetes, the effectiveness of the insulin per unit varied inversely with the quantity used.

TABLE 6—*Effect of Insulin During Period of Acidosis, All Insulin Given Subcutaneously*

Date	Hour	Food			Insulin Units	Blood Sugar		Comment
		P	F	C		Mg Per Cent		
Oct 15	8 00 a m	6	6	10				
	12 00 a m	4	6	12				
	5 00 p m	5	6	10				
Oct 16	9 00 a m				50	480		Nausea and vomiting
	10 00 a m					538		Kussmaul breathing
	10 30 a m					510		
	11 30 a m					514		
	1 00 p m				50	576		No improvement
	1 40 p m				200			No improvement
	4 00 p m				200			Digifolin, hypodermoclysis
	4 20 p m					614		Almost pulseless, vomiting
	6 00 p m				200			Digifolin, no improvement
	9 00 p m				200			No improvement
Oct 17	1 00 a m							Hypodermoclysis
	8 00 a m				200			
	12 00 a m	20	29	19	65			Feels much better
Oct 18	5 00 p m	15	32	25	65			Bright and cheerful
	8 00 a m	14	29	25	65	60		Light sweat
	12 00 a m	16	32	22	65	88		
	5 00 p m	16	28	23	65	60		Light sweat
Oct 19	7 00 a m				50	58		Sweating
	8 00 a m	11	29	21				
	12 00 p m					390		Feels well

The patient remained under observation at the Jewish Hospital from September 10 to Dec 4, 1926. During all of this time she was on a varying but greatly restricted diet, the maximum intake on any one day being protein, 75 Gm, fat, 150 Gm and carbohydrate, 100 Gm. While her response to insulin varied somewhat, she constantly required unusually large doses of insulin, not to keep her urine sugar free, for that was possible for only a few hours at a time, but to keep her reasonably comfortable. Every attempt to reduce the dose of insulin was promptly followed by an alarming ketonuria and, if persisted in, by symptoms of impending coma. The average daily dose of insulin while she was in the hospital was 317 units, a total of 26,965 units in less than three months. Repeated attempts were made to reduce the dose. Each time, however, an alarming acidosis supervened, from which the patient could be rescued only by the administration of enormous amounts of insulin. Thus, on November 9, 1,000 units of insulin had to be given in broken doses, on November 12, 1,100 units were given, 300 subcutaneously and 800 intravenously. For a period of several days, beef insulin was used instead of the usual hog insulin, no difference in the effect could be noted.

From time to time, the manner of administration was modified, in the hope of rendering the insulin more effective. Thus, during the first week in October

the patient was put on a diet of protein, 75, fat, 50 and carbohydrate, 105 Gm, 50 units of insulin were given subcutaneously before breakfast, and ten hourly injections of from 10 to 20 units were given during the day. The patient was never made sugar-free for more than an hour, and the total effect on blood and urine sugar was definitely less than when one or two large doses were given. The observations made October 7 (table 7) illustrate her lack of response to this therapy.

After four days of this method of treatment, it was discontinued, both because it was ineffectual and because the patient objected to the numerous injections. The best results were finally obtained when a single large dose of insulin, from 240 to 400 units, was given before breakfast with a diet consisting of protein, 75 Gm, fat, 150 Gm and carbohydrate, 100 Gm. A moderate glycosuria persisted, to be sure, and the blood sugar remained high, but the patient felt comfortable and gained in weight and strength.

Early in December, she was allowed to go to her home in the country, on this diet, with instructions to give herself an injection of 240 units of insulin

TABLE 7—*Lack of Response of Patient to Insulin Therapy*

Time	Insulin (Units)	Food			Blood Sugar	Urine Sugar (Gm per Hour)
		Protein	Fat	Carbo- hydrate		
7 30 a m	50				292	
7 30 a m					341	
8 00 a m					284	
9 00 a m					304	0.5
10 00 a m	40	25	50	35	300	1.0
11 00 a m	20					2.2
12 00 p m	20					3.1
1 00 p m	20	25	50	35		1.8
2 00 p m	20					1.5
3 00 p m	20					9.0
4 00 p m	20					1.8
5 00 p m	20	25	50	35		2.7
6 00 p m	20					1.0
7 00 p m						5.0
8 00 p m						4.5
9 00 p m						4.0

every morning. Six days later, she returned with the statement that on this regimen her urine had remained sugar-free and that she had been having increasingly severe hypoglycemic reactions. A few days' study in the hospital showed that, while the blood sugar during fasting remained more than 200 mg per cent, the glycosuria could now be controlled by a daily dose of 175 units of insulin. At a later visit in February, the dose could once more be reduced to 128 units. Since then she writes that she has felt entirely well and finds no difficulty in doing her full work as a school teacher. On a single dose of 104 units of insulin in the morning, her urine is constantly free from sugar and she occasionally has a mild hypoglycemic reaction. The dose could probably be cut down still further, but she cannot spare the time to come to St. Louis for further study. It would appear that her condition is now that of a moderately severe diabetes of the usual type.

COMMENT

In considering the behavior of this patient toward insulin several plausible explanations suggested themselves. One was the possible presence in her blood of some substance, perhaps an antinsulin, capable of inactivating all but excessive doses of the hormone. In order to

determine this, 10 cc of the patient's blood serum was added to the minimum amount of insulin required to produce hypoglycemia in fasting rabbits and the mixture injected into two such animals. If an anti-insulin had been present in the blood, the rabbits should have failed to respond by hypoglycemic reactions. The effect on the rabbits was, however, just the same as though the insulin had been injected without the admixture of the blood. The presence of an anti-insulin was thus disproved.

In view of the fact that the patient had repeatedly shown allergic phenomena following the injection of insulin, the possibility that the insulin may have been destroyed in the tissues by some anaphylactic process had to be considered. However, aside from the difficulty of explaining the destruction in this manner of the large doses given, we failed to demonstrate the constant presence of any action of this kind. The intracutaneous injection of insulin in high concentration did not cause a local reaction, and the blood serum did not show any trace of a precipitin reaction with insulin containing 240 units per cubic centimeter.

It has been stated that insulin is rapidly and almost quantitatively excreted in the urine, provided the kidneys are normal. With the relatively small doses ordinarily administered in human cases, the detection of insulin and especially its quantitative determination in the urine are difficult and are fraught with many possibilities of error. In our patient, the unusually large doses given should have made it easy to detect insulin in the urine, if Carlson's view is correct. On two occasions, once after the administration of 50 units in a single dose, intravenously and after fasting, and again after the subcutaneous injection of 900 units within twelve hours without food, the urine was carefully examined. The total amount was concentrated, salted out by saturation with ammonium sulphate, the precipitate obtained fractionated by iso-electric precipitation, and every fraction, the iso-electric precipitate as well as the mother liquor, was tested on rabbits. No action of insulin whatever could be made out. This shows definitely that in our patient, at any rate, an appreciable amount of insulin was not lost through the kidneys.

These considerations lead us to the belief that the peculiar reactions shown by our patient can best be explained by assuming that her diabetes was not due exclusively to pancreatic insufficiency but to the lack of some substance other than insulin and equally necessary for the metabolism of carbohydrates.

This explanation, also suggested by Falta in his case referred to, is in accord with current theories, based on a large volume of experimental work. Thus according to Brugsch and Horsters,¹⁷ tissues of the muscle and liver and other tissues contain a synthesizing

17 Brugsch T, and Horsters H. Phosphatase and Phosphatase of the Hexose-Diphosphoric Acid, *Biochem Ztschr* **155** 459, 1925.

enzyme, "phosphatase," which converts glucose into hexose-diphosphate (the lactacidogen of Embden and his school), as a necessary step in its catabolic utilization. Phosphatase, according to Brugsch, is in itself inactive without the presence of insulin, which "seems to be a kinase, capable of activating it." This view is supported by the fact that when sugar disappears from the blood under the action of insulin, phosphoric acid, too, is simultaneously withdrawn from the circulation.¹⁸

Lundsgaard and his associates¹⁹ also claim to have demonstrated the presence of an enzyme in muscle, which reacts with glucose only in the presence of insulin. The reaction in this triangle of substances is, however, entirely different from that assumed by Brugsch. It consists in the transmutation of the ordinary α - β glucose into a reactive isomeric form, which they call "neo-glucose" and which alone can be utilized by the tissues. The muscle enzyme, which they call "insulin complement," and insulin itself must be present simultaneously to bring about this change.

Ahlgren²⁰ approached the problem from a somewhat different angle, by employing Thunberg's methylene-blue technic, but arrived at substantially identical conclusions. His long array of convincing experiments in vitro demonstrates that fresh tissue from muscle contains an enzyme, "glycomutin," which in the presence of insulin changes the ordinary glucose into a more reactive form.

In the light of these experiments, we deem it at least possible that in our patient the obstinacy of her hyperglycemia was caused not so much by a lack of production of insulin as by an insufficiency of the muscle enzyme (phosphatase, insulin complement, glycomutin). The fact that enormous doses of insulin were finally effective can be explained by the law of mass action which, to a certain extent, is valid, also in enzymatic and immunologic reactions. We assume that the normal concentration of the muscle enzyme was cut down by some functional disturbance and that the huge doses of insulin were required in order to compensate for this deficiency. A similar phenomenon is sometimes observed in the relationship between complement and sensitized. The patient's final and so far permanent improvement would then be accounted for by the restoration of the temporarily impaired supply of the muscle enzyme to its normal concentration. The foregoing hypothesis also accounts satisfactorily for our patient's

18 Briggs, A. P., Koechig, I., Doisy, E. A., and Weber, C. J. Some Changes in the Composition of Blood Due to the Injection of Insulin, *J. Biol. Chem.* **58** 721, 1924.

19 Lundsgaard, C., and Holboell, S. A. Effect of Insulin and Muscle Tissue on Glucose in Vitro, *J. Biol. Chem.* **62** 453, 1924, **70** 71, 1926. Lundsgaard, C., Holboell, S. A., and Gottschalk, A. *Ibid.* **70** 89, 1926.

20 Ahlgren, G. Insulin and Tissue Oxidation, *Skandin. Arch. f. Physiol.* **47** 149, 1925 (supp.)

failure to respond to broken doses of insulin. It has frequently been observed and has been shown experimentally by Holm²¹ that, in ordinary cases of diabetes, repeated small doses of insulin affect the blood sugar far more profoundly than the same total dose administered in a single injection. In our case, however, from 200 to 300 units of insulin, distributed into 10 or more injections in the course of the day (table 7) were definitely less effective than a similar dose administered as a single injection. It seems difficult to avoid the conclusion that the principle of mass action must play a part here and, if so, that the patient's condition must be due to a lack of muscle enzyme or of some similar agent and not to the pancreatic secretion alone.

SUMMARY

A case of diabetes mellitus is reported, which showed the following peculiarities

- 1 Beginning as a mild case, it rapidly became more severe and at one time showed an allergic reaction to insulin

- 2 For a period of some months, the patient proved relatively refractory to insulin, responded only to enormous doses of insulin and slipped into coma or precoma as soon as these doses were reduced

- 3 During this period, the patient did not respond better to fractional doses of insulin than to an equivalent single dose. On the whole, the latter was more effective than the former. In ordinary diabetes, the reverse is true

- 4 To a moderate degree, the patient's response to insulin seemed to be increased by the simultaneous injection of parathyroid extract

- 5 Later, the response to insulin increased, and the case again became an ordinary, moderately severe diabetes

- 6 It is shown that the patient's failure to respond in the usual manner to insulin can be explained neither by a destruction of insulin in the body nor by its excretion in the urine

- 7 It is suggested that in this case, as perhaps in other similar ones reported in the past few years, the diabetes was due not only to a lack of pancreatic secretion, but also to a lack of muscle enzyme (phosphatase, insulin complement, glycomutin)

If our conclusions are confirmed by the observation and study of similar cases, we may be justified in assuming the existence of at least two varieties of diabetes mellitus: the one due to pancreatic disease and responding to insulin, the other due to a deficiency in the production of a muscle-enzyme and relatively refractory to insulin.

²¹ Holm, K. On the Quantitative and Optimal Action of Insulin, *Klin Wchenschr* 5 2157 (Nov 12) 1926

VITAL CAPACITY OF CHINESE STUDENTS *

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NEW YORK

The last decade has seen a revival of interest in the subject of vital capacity as a diagnostic and prognostic measure. This interest has been accompanied by an increased output of literature on the subject, much of which has been of practical as well as of scientific value. This paper presents the results of a study of the vital capacity of Chinese students similar socially to the American groups studied by Hastings,¹ Baldwin,² Hitchcock³ and others. The results may be directly compared with analogous American data.

A comprehensive review of the literature on vital capacity was presented by Dr J A Myers⁴ in the excellent monograph, "Vital Capacity of the Lungs." Hence I shall dispense with a historical discussion of the study of vital capacity and with a review of the literature in this paper and proceed to the subject indicated in the title. This study was made during the last three years, while I was in charge of the professional school of physical education of the National Southeastern University of Nanking, China.

SUBJECTS OF STUDY

The men of this study are divided into three groups. The first group includes 1,151 men students of the National Southeastern University of Nanking, China. These students had an average height of 168 cm (66 inches) and an average ponderal index, in metric units, of 22.4. They are about 10 per cent lighter in weight than Americans of the same age and height. The latitude of Nanking is approximately that of Savannah, Ga., and Nanking probably has a slightly higher average humidity.

Members of this student body have engaged in a normal amount of athletics since becoming college students, and have largely come from middle schools in which exercise was required to about the same extent as in the schools of the United States about ten years ago. Their play

Department of Physical Education National Council Y M C A

1 Hastings, W W. Manual of Physical Measurements, 1902. Seaver, J W. Anthropometry and Physical Examination, published by author, 1909, p 110.

2 Baldwin, B T. The Fifteenth Yearbook of the National Society for the Study of Education, page 11, part 1, Chicago, University of Chicago Press, 1916.

3 Hitchcock, Edward in Seaver. Anthropometry and Physical Examination, published by author, 1919, p 90.

4 Bibliography in Myers, J A. Vital Capacity of the Lungs. Baltimore, Williams & Wilkins, 1925.

life as children has been less active than that of American children of the same ages. The standards of vital capacity proposed will be largely comparable with American student anthropologic statistics of the kind that are available in the tables chosen for comparison. These students come predominantly from the Yangtse Valley, though, in lesser numbers, they represent all of China.

The second group is composed of about 400 students from the elementary and middle schools attached to the Teachers College of the National Southeastern University of Nanking. The comments on the first group would apply to these students as well, except for the fact that the students of the elementary school are almost all from Kiangsu Province.

The third group includes 2,458 students from Hongkong. These students range from 5 to 19 years of age. They are all "Cantonese," and represent the subtropical group of Chinese. They are anthropologically different from the Kiangsu Chinese and, as will be seen, show differences in vital capacity. The measurements of these students were made available to me by A. E. Dome, physical director of the Y. M. C. A. in Hongkong.

Two groups of women were studied. The first included 131 college students of the National Southeastern University and of Ginling College, both of Nanking. (For these records I am indebted to Miss K. J. Ku of the National Southeastern University, and to Miss Emily I. Case of Ginling College.)

The second group was made up of 576 girl students of the elementary and middle schools of Nanking, measured by Miss Lung-yuan Du, a research student working under my direction.

PURPOSES OF THIS STUDY

The objectives of this study may be outlined as follows:

- 1 To determine the best basis for the prediction of normal vital capacity
- 2 To determine the normal variability in the vital capacity of the Chinese
- 3 To ascertain the relationship of "chest expansion" to vital capacity
- 4 To ascertain whether or not there was a relationship between overweight and underweight and vital capacity in the Chinese
- 5 To determine statistically normal standards of vital capacity for Chinese students and to present tables for the "normal" vital capacity
- 6 To compare the vital capacity of the Chinese of different anthropologic groups, specifically, to compare the vital capacity of Southern Chinese with that of East Central Chinese
- 7 To compare the vital capacity of the Chinese with that of Americans of the same social class

In the studies presented here, it should be noticed that all measurements of vital capacity represent the volumes obtained with the water in the spirometer at room temperature. I have found that the ordinary

wet spirometer as I used it (the instrument manufactured by the Narragansett Machine Company) varied in the volume recorded according to the temperature of the water.⁵ When the tube running up through the water was altered to offer more surface area per unit of cross-section, the volume recorded by the instrument varied exactly with the volume to be expected when corrected for temperature and vapor pressure. As the air expired is approximately 37 C in temperature and saturated with water vapor, this correction gives a volume at the various temperatures as recorded in table 1. The volumes given in this article have not been corrected for this change in volume, as it is thought that most recorded volumes will be taken with water at room temperature. The water in the spirometer was approximately 18 C, and the error for that temperature should not be larger than 1 or 2 per cent.

TABLE 1—*Proportionate Volumes of Air Expired into a Spirometer with Water at Different Temperatures**

Temperature	Per Cent by Volume	Temperature	Per Cent by Volume	Temperature	Per Cent by Volume
37	100.00	24	92.59	11	87.06
36	99.83	23	92.12	10	86.68
35	98.65	22	91.65	9	86.30
34	98.04	21	91.20	8	85.93
33	97.63	20	90.75	7	85.57
32	96.83	19	90.31	6	85.20
31	96.26	18	89.88	5	84.81
30	95.69	17	89.46	4	84.40
29	95.14	16	89.04	3	84.14
28	94.61	15	88.63	2	83.79
27	94.09	14	88.23	1	83.45
26	93.58	13	87.81		
25	93.08	12	87.44		

* To correct, the volume is divided by the percentage given. All temperatures are given in centigrade.

MOST SATISFACTORY BASIS FOR THE PREDICTION OF NORMAL VITAL CAPACITY

The variables generally used in endeavoring to predict vital capacity have been height, weight, girth of chest and surface area. I have made various trials with these variables and also with combinations of height and weight computed from multiple correlations. In computing multiple regressions, it will be readily seen that the regression of height on weight will be far too curvilinear to use in computing multiple correlations according to the usual formulas. I have tried to avoid this difficulty to some extent by cubing the height. This did not entirely avoid the trouble, but it did give regressions much more linear than would have otherwise been the case. The results obtained in this part of the study were as follows:

5 McCloy, C. H. On Using the Spirometer as an Instrument of Precision, American Physical Education Review, May, 1927.

Students of the National Southeastern University, and the Southeastern University Middle School and Elementary School—In all results given, the usual symbols are used. The letter “ r ” represents the correlation coefficient, “ η ” represents the correlation ratio for curvilinear material, “ σ ” represents the standard deviation. Subscripts will be explained.

a Southeastern University men students

Height and vital capacity	$r = 0.433 \pm 0.025$
Weight and vital capacity	$r = 0.566 \pm 0.020$

Partial correlations according to the usual methods for rectilinear regressions gave the following figures

Height and vital capacity, weight partialled out	$r = 0.1169 \pm 0.0247$
Weight and vital capacity, height partialled out	$r = 0.4205 \pm 0.0239$

In both these cases, the curvilinearity of the regressions of height on weight and of height on vital capacity prevented the figures from being significant. It is more significant, however, than would be the case with a larger range of ages, as in the other data given. Another attempt to partial out height was made by correlating the cube root of the weight divided by height with the cube root of the vital capacity divided by height. The correlation coefficient was 0.350 ± 0.021 .

The attempt to secure a multiple correlation with not too high a degree of curvilinearity resulted as follows (numbers in each case being 1,160)

Weight and (height) ³ ,	$r = 0.5635 \pm 0.0135$
Weight and vital capacity,	$r = 0.5396 \pm 0.0140$
Vital capacity and (height) ³ ,	$r = 0.4634 \pm 0.0155$
With Yule's' multiple regression,	$r = 0.4723 \pm 0.0155$

Clearly this multiple regression is thrown out by the curvilinearity of the two-variable intercorrelations, and is less than the correlations with height and weight alone. I shall, therefore, not discuss it further in this paper.

The next variable tried was girth of chest. This was taken at the level of the base of the ensiform and represented the mean of measurements taken at full inhalation and exhalation. Girth of chest and the cube root of vital capacity $r = 0.441 \pm 0.019$. That this was not greatly dependent on height was demonstrated by correlating girth of chest divided by height against the cube root of vital capacity divided by height, $r = 0.407 \pm 0.020$.

6 Yule, G. Udny. *An Introduction to the Theory of Statistics*, C. Griffin and Co., 1924, p. 233. Kelley, Truman. *Statistical Method*, New York, The Macmillan Company, 1923, p. 283.

An attempt was made to secure a combination index which would represent girth of chest and height together. This was done by correlating the vital capacity against the "normal" weight for height and body build according to the method I developed.⁷ In this standard, the normal weight is taken from height and mean girth of the chest. This correlation proved to be slightly less than for weight alone, being $r = 0.5580 \pm 0.0165$.

The correlation⁸ of vital capacity with surface area, computed by the Dubois formula, gave in each case the best results. With the college students, a homogeneous group, the correlation was $r = 0.6006 \pm 0.0127$.

With a group of elementary school, middle school and college men, the correlation of vital capacity with surface area was as follows:

$$r = 0.9122 \pm 0.0043 \quad \eta = 0.9147 \pm 0.0042 \quad N(\eta^2 - r^2) = 3.16$$

which is far within the bound of linearity according to Blakeman's criterion. This large correlation is partly spurious, owing to the wide range of ages involved, and no one age would give nearly as large a correlation coefficient. It is significant, however, that the regression is linear and that the normal standards may be predicated on the regressions found. This correlation with surface area was so much larger than with any one variable that it is obviously the most satisfactory device I have tried.

Hongkong Students—Correlations obtained were as follows:

Height and vital capacity	$r = 0.7822 \pm 0.0054$
Weight and vital capacity	$r = 0.8055 \pm 0.0048$
(Height) ² and vital capacity	$r = 0.8311 \pm 0.0042$
(Height) ² and weight	$r = 0.8990 \pm 0.0026$

Individual partial correlations, though not reliable, owing to the curvilinearity of the data, were nevertheless computed and gave the following results:

$$r_{h^2 \cdot v \cdot w} = 0.4046 \pm 0.0114 \quad (\text{"h"}^2 \text{ denotes (height)}^2, \text{"w"} \text{ denotes weight,} \\ r_{w \cdot h^2} = 0.2517 \pm 0.0134 \quad \text{and "v" denotes vital capacity})$$

These results are just opposite to those found with the Southeastern University data, in which weight gave the greater partial correlation. Owing to the curvilinearity, multiple regressions were not calculated.

⁷ McCloy, C. H. Weight Standards for the Individual, American Physical Education Review, September, 1926.

⁸ DuBois and DuBois. Clinical Calorimetry, Tenth Paper. Arch. Int. Med. 17: 863 (June) 1916.

Surface area correlated with vital capacity as follows

$$r = 0.8370 \pm 0.0045 \quad \eta = 0.8493 \pm 0.0038 \quad N = 2,458$$

This is the highest correlation obtained, but is not greatly higher than that obtained with height cubed. All Hongkong correlations are spuriously high, owing to the wide range in age. According to Blakeman's criterion, this would not fall within the bounds of linearity. The line of the means of the arrays, however, follows closely that of the regression line, and I do not believe that Blakeman's criterion in such a case, having such a large number, is necessarily valid. Means of arrays which slightly zigzag up the regression line owing to chance errors of the small numbers in an array will give a smaller correlation coefficient, but the best fitting line may still be a straight line. The correlation ratio, however, will be large in comparison to the correlation coefficient and will fall outside of Blakeman's criterion. It seems to me that this is the case in this correlation.

Nanking Guls and Women—Correlations obtained with college women were as follows

Weight and vital capacity	$r = 0.376 \pm 0.051$
Height and vital capacity	$r = 0.394 \pm 0.049$
Surface area and vital capacity	$r = 0.4999 \pm 0.044$

The correlation obtained with elementary, middle school and college girls combined is as follows: surface area and vital capacity, $r = 0.6064 \pm 0.0178$ $\eta = 0.6168 \pm 0.0174$ $N(\eta^2 \cdot 1^2) = 7.37$, which would indicate linearity of regression.

It would seem from these data that in each case surface area is the most satisfactory method of predicting vital capacity of the Chinese groups studied. With the charts given by Dubois or by the logarithms that I have prepared, this may be conveniently computed, and in addition it gives the greatest accuracy of prediction.

NORMAL VARIABILITY OF THE VITAL CAPACITY IN THE CHINESE

The variation of all records of men from the statistical norm was computed. The probable error of the distributions of the arrays averaged 8.8 per cent of the mean. This was computed from a group of 4,402 cases, including all Nanking and all Hongkong cases. This, however, is only the probable error, that is, this represents a deviation in which approximately half of the cases fall outside the limits. This is a greater deviation than is comfortable for predictive purposes. It should be the aim of future investigation to discover some method which will cut this large error to smaller dimensions. For university students alone, this error was 6.8 per cent of the mean.

RELATION OF "CHEST EXPANSION" TO VITAL CAPACITY

It has been the custom of insurance examiners and of some other physicians to utilize the difference in girth of the chest at full expansion and full contraction as a measure of vital capacity. I wished to determine the validity of this procedure for Chinese students.

A previous experiment that I⁹ made demonstrated conclusively that measurement of the chest at the level of the nipples was not a reliable measurement and that the best measurement was that taken at the level of the base of the ensiform. Measurement at the nipple line includes the pectoralis major and the latissimus dorsi and, in women, the variable factor of the mammary gland. A slight contraction of the muscles named will make a large spurious difference in girth of the chest. I know many men who can attain an "expansion" of fully 6 inches with no movement of air into the lungs, when the tape is at the level of the nipple. There is little spurious expansion at the level of the ensiform. Hence, all measurements were taken at that level.

A correlation of vital capacity with chest expansion gave a correlation coefficient of 0.3214 ± 0.0256 in 553 male college students. This is, however, a spuriously high correlation, for it was found that expansion was approximately 10.8 per cent of the girth of the chest for all sizes of college students. Since mean girth of chest correlates 0.441 with vital capacity, a large chest would usually be accompanied by a larger vital capacity, as well as by a larger expansion, and this would give a spuriously high correlation.

Both vital capacity and chest expansion were next reduced to a common height level. A correlation of the chest expansion divided by height and the cube root of the vital capacity divided by height gave a correlation coefficient of only 0.1260 ± 0.0599 , which, according to the usual criterion that the coefficient should be three times as large as its probable error, is not significant. This would indicate that chest expansion was not a safe guide to vital capacity in the Chinese student. This was not tried with women, but I have obtained a correlation coefficient, using the same procedure on the data from American women, of 0.3068 ± 0.0331 . This is much higher, but is not an indication of a real relationship which would make safe prediction easy.

RELATIONSHIP OF VITAL CAPACITY TO NUTRITION

In this study, normal weight for height and body type was computed from my tables.⁷ The amount overweight or underweight was then computed and correlated against the cube root of the vital capacity divided by the height. The correlation coefficient was 0.158 ± 0.028 with

⁹ McCloy, C. H. Ts'e-liang Fei Pu-ti Yen-chiu (Studies on Measurement of the Lungs). Chinese Journal of Physical Education and Hygiene, Shanghai, Commercial Press, 1925, vol. 3, no. 4. (In Chinese.)

537 men. The probable error of this correlation is well within the limits of one-third the correlation coefficient. While this correlation is small, it seems to us to have some significance. In the first place, weight was estimated not only for height, but also for body build. I have demonstrated⁷ that this reduces the chance error from more than 7 per cent to about 2.4 per cent. In the second place, weight and lung capacity vary, independently, no small amount, hence there would normally be a wide scatter in correlation. I believe that this small correlation is not altogether insignificant and that it indicates that there may be some causal relationship between undernourishment and small vital capacity or vice versa, or that there may be a common factor causing both.

NORMAL STANDARDS OF VITAL CAPACITY FOR CHINESE STUDENTS
WITH TABLES FOR PREDICTING INDIVIDUAL
NORMAL VITAL CAPACITY

Certain studies of vital capacity have postulated a standard based on a constant times the surface area or times the height. Thus, West¹⁰ proposes a standard for men of 2.5 liters per square meter of surface area. My results would seem to point to the conclusion that, with the high degree of rectilinearity found, the regression line of the correlation between vital capacity and surface area is a more dependable device, for the ratio of surface area to vital capacity changes at different ages and sizes of man. In the correlations which I obtain with Chinese data, the differences between the correlation coefficient and the correlation ratio are small and fall within the normal limits of a variability due to chance. In other words, even for comparatively large age ranges the regression is quite linear.

As will be seen in the tables, the standards obtained for college students in each case are slightly larger than for those below the college ages. I have some data, too incomplete for publication, which would indicate that there is an increase with the onset of the postpubescent period. In medical examinations, it is usually feasible to ascertain the "physiologic age"¹¹, hence it might be in order to secure data, dividing the groups at the age of either the onset of pubescence or the completion of the pubescent period and the beginning of postpubescence, and to present separate standards for the two groups. This would undoubtedly give more accurate standards for those near this age. In the standards presented here, this has not been done. I believe that the college standards may be used for all those of an age of postpubescence, while the standards given for others may be used for the prepubescent.

¹⁰ West, H. F. Clinical Studies on the Respiration. VI, Arch. Int. Med. 25: 306 (March) 1920.

¹¹ Crampton, C. W. Physiological Age, American Physical Education Review, March, 1908.

Essential Data for Computation of Tables—College men of East-Central China

Mean surface area 1 570 square meters
Mean vital capacity 3 324 liters
Correlation coefficient $r = 0.6006 \pm 0.0127$
Equation of regression line $VC = 3.105 (SA) - 1.551$

Elementary, High School and College Students of East Central China (About one-fifth were college students) The correlation table for this group is shown in chart 1. On this chart, I have plotted the regression line for this group, and for comparison, the regression line for college students. It will be seen that the regression for the college

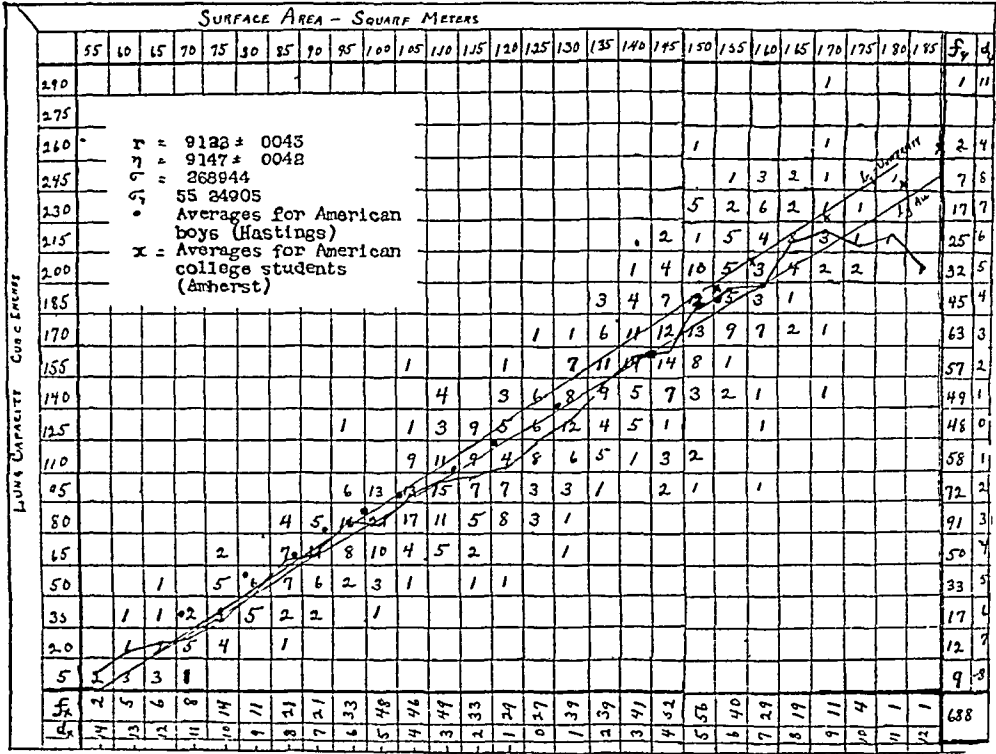


Chart 1—Scatter diagram for Nanking students of all groups

students runs slightly higher than that for the other group. On this chart, I have also indicated averages for American students. The dots are the medians for a given age, height and weight, taken from Hastings¹. The ages range from 6 to 16. Those marked with a "x" represent medians of Amherst students, taken from Hitchcock's² data. It will be seen that there is little difference between American and Chinese data.

Mean surface area 1 260 square meters
Mean vital capacity 2 129 liters
Correlation coefficient $r = 0.9122 \pm 0.0043$
Correlation ratio $\eta = 0.9147 \pm 0.0042$
Equation of regression line $VC = 3.063 (SA) - 1.71038$

South China Students (Hongkong) The correlation scatter diagram of this group is given in chart 2. This regression is not absolutely linear, but is close to linearity. Owing to the acceleration at the age of puberty, one would expect to find that the line of means of the arrays would take an upward slant at about that period. This does not prove to be the case, however. On the scatter diagram, I have indicated the line of means of vital capacity by dotted line.

Mean surface area	1 247 square meters
Mean vital capacity	2 122 liters
Correlation coefficient	$r = 0.8370 \pm 0.0045$
Correlation ratio	$\eta = 0.8493 \pm 0.0038$
Equation of regression line V C	$= 2.3676 (S A) - 0.830397$

Women of East-Central China The number of cases of college women was not sufficiently large to give trustworthy results, but they are given, together with comparisons with other data, for what they may be worth.

Mean surface area	1 4257 square meters
Mean vital capacity	2 0477 liters
Correlation coefficient	$r = 0.4999 \pm 0.0442$
Equation of regression line V C	$= 1.6595 (S A) - 0.317$

All Girl Students The scatter diagram of the correlation is given in chart 3. On this table, I have plotted the regression for this chart, and also the regression for the college students alone. Medians for American students are also plotted thereon. These will be referred to subsequently. The regression of this table is linear.

Mean surface area	1 321 square meters
Mean vital capacity	1 797 liters
Correlation coefficient	$r = 0.6064 \pm 0.0178$
Correlation ratio	$\eta = 0.6168 \pm 0.0174$
Equation of regression line V C	$= 1.7112 (S A) - 0.463$

Standards of vital capacity for each group are readily computed for each surface area by means of the regression equations. In table 2 I give the vital capacity for each group in metric units, and in table 3 the same is given in English units.

Owing to the fact that the smallest children seldom understand how to attain to their best record in vital capacity, it is probable that vital capacities for children with a surface area of less than 0.75 square meters are not to be relied on. Regressions obtained for this group are probably also not particularly accurate, hence the low values of these tables are questionable.

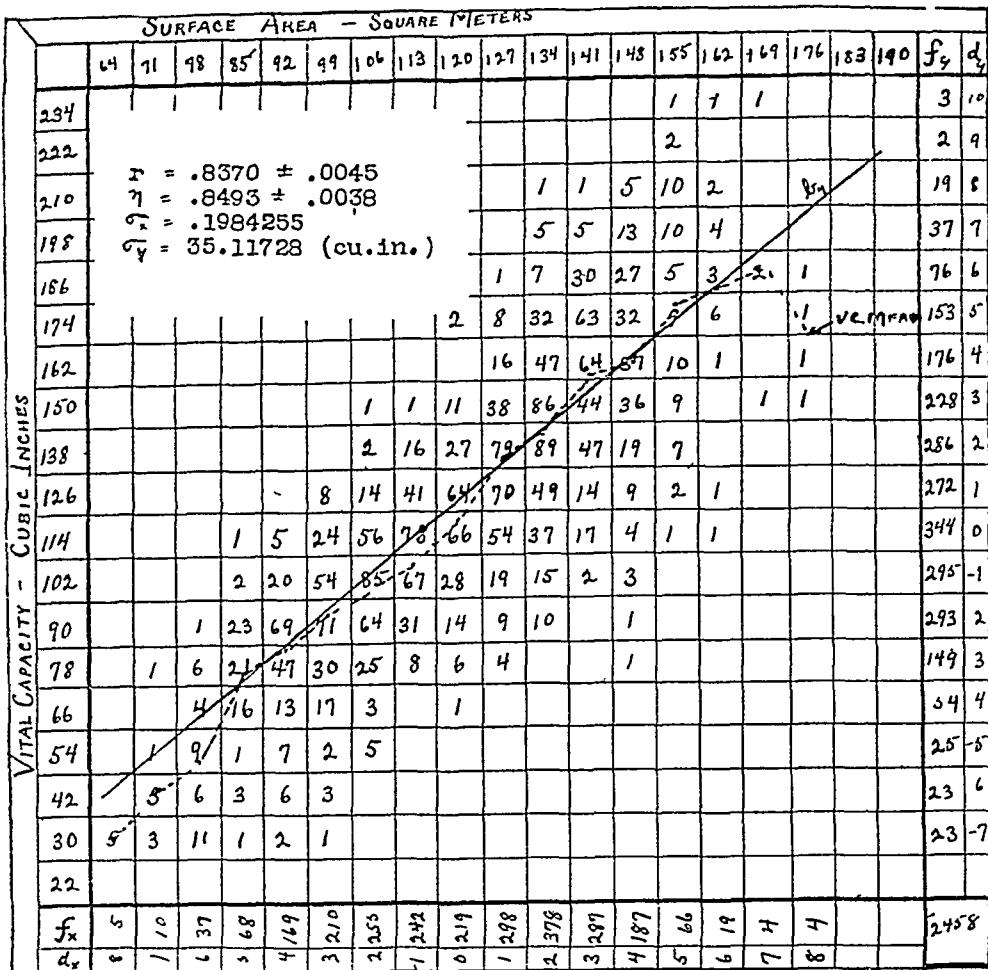


Chart 2—Scatter diagram for all Hongkong students

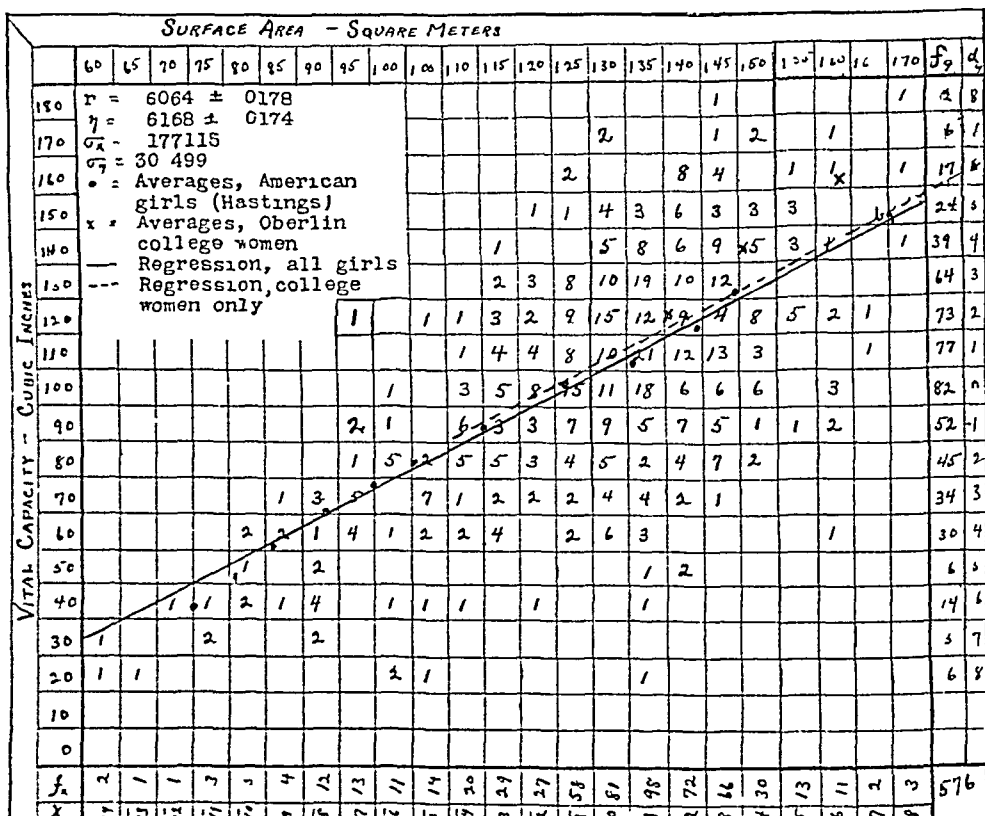


Chart 3—Scatter diagram all girls of Nanking, including college ages

TABLE 2—*Vital Capacity Norms for the Different Chinese Groups (Metric—liters)*

Surface Area	East China College Men	Elementary and High School Boys	Hongkong Boys	College Girls	All East China Girls
2.25	5.44	5.18	4.50		
2.20	5.28	5.04	4.38		
2.15	5.12	4.87	4.26		
2.10	4.97	4.72	4.14		
2.05	4.81	4.56	4.02		
2.00	4.66	4.41	3.90	3.00	
1.95	4.50	4.25	3.79	2.92	
1.90	4.35	4.09	3.67	2.84	
1.85	4.19	3.94	3.55	2.75	
1.80	4.04	3.78	3.43	2.67	2.62
1.75	3.88	3.63	3.31	2.59	2.53
1.70	3.73	3.47	3.19	2.50	2.45
1.65	3.57	3.32	3.08	2.42	2.36
1.60	3.42	3.16	2.96	2.34	2.27
1.55	3.26	3.01	2.84	2.26	2.19
1.50	3.11	2.85	2.72	2.17	2.10
1.45	2.95	2.70	2.60	2.09	2.02
1.40	2.80	2.54	2.48	2.01	1.93
1.35	2.64	2.39	2.37	1.92	1.85
1.30	2.49	2.23	2.25	1.84	1.76
1.25	2.33	2.08	2.13	1.76	1.68
1.20	2.18	1.92	2.01	1.67	1.59
1.15	2.02	1.77	1.89	1.59	1.50
1.10	1.86	1.61	1.77	1.51	1.42
1.05	1.71	1.46	1.66	1.43	1.33
1.00	1.55	1.30	1.54	1.34	1.25
0.95		1.14	1.42		1.16
0.90		0.99	1.30		1.08
0.85		0.83	1.18		0.99
0.80		0.68	1.06		0.91
0.75		0.52	0.95		0.82
0.70		0.37	0.83		0.73

TABLE 3—*Vital Capacity Norms for the Different Chinese Groups (English units—cubic inches)*

Surface Area	East China College Men	Elementary and High School Boys	Hongkong Boys	College Girls	All East China Girls
2.25	332	319	274		
2.20	322	310	267		
2.15	313	300	260		
2.10	303	291	253		
2.05	294	281	246		
2.00	284	272	238	183	
1.95	275	262	231	178	
1.90	265	253	224	173	
1.85	256	243	217	168	
1.80	246	234	209	163	160
1.75	235	224	202	158	155
1.70	227	215	195	153	150
1.65	218	205	188	148	144
1.60	209	196	180	143	139
1.55	199	186	173	137	134
1.50	190	177	166	132	129
1.45	180	168	159	127	124
1.40	171	158	152	122	118
1.35	161	149	144	117	113
1.30	152	139	137	112	108
1.25	142	130	130	107	103
1.20	133	120	123	102	97
1.15	123	111	115	97	92
1.10	114	101	108	92	87
1.05	104	92	101	87	82
1.00	95	82	94	82	77
0.95		73	87		71
0.90		63	79		66
0.85		54	72		61
0.80		44	65		56
0.75		35	58		51
0.70		25	50		45

VITAL CAPACITY OF SOUTHERN CHINESE COMPARED TO THAT OF CHINESE OF EAST CENTRAL CHINA

A glance at the tables and charts and at the respective regression equations will show the differences found. It is seen that in the smaller surface areas, the vital capacity of the Hongkong Chinese exceeds that of the East Central Chinese. The latter, however, soon pass the Hongkong boys, and after that, they keep their advantage. This fact is in keeping with the observations of Dr. Stevenson,¹² who found that the southern Chinese matured earlier, and that their height and weight exceeded that of the Northerners during the early years, only to be passed near the age of puberty by the Chinese of Central and of North China. I have no data on the vital capacity of the northern Chinese to compare with that of the Southerners.

VITAL CAPACITY OF CHINESE STUDENTS COMPARED TO THAT OF AMERICAN STUDENTS

The studies made on American students have differed in no small degree. I have chosen for comparison the data presented for younger children by Hastings¹ and those of college students by Hitchcock. These measurements were made at a time in the history of American schools when physical education had not attained the prevalence or intensity that it shows today, hence the comparison would correspond more closely to the type of environment of the Chinese student of today so far as his physical activity is concerned. The marks plotted on charts 1 and 3 show graphically the more important facts for men students. It should be noticed that the standards for Chinese were taken from the regressions of vital capacity on surface area, and those for American students computed from the medians of various age groups, hence the standards are not necessarily strictly comparable, for it is not possible to weight medians. I do not believe that this will introduce a serious error, however, for this type of distribution is approximately normal.

In chart 3 it will be noticed that while the curves for Chinese girls and those for American girls are almost superimposed, the vital capacities of the women of Oberlin College runs above that of Chinese college women. This, possibly, about represents the difference in the activity of the two groups. Chinese college women largely represent a group that has grown up with little exercise. The pupils of the elementary and high schools, on the other hand, represent a newer generation. They have had much more exercise than the preceding school generation. Nothing authoritative can be said, however, in the way of interpretation.

¹² Stevenson, Paul H. Collected Anthropometric Data on the Chinese, China M. J. 39:855 (Oct.) 1925.

In addition to the data presented here, I have approximately fifty records for Chinese athletes. These men differ greatly both in surface area and in vital capacity, and the number of the men is so small as to render a correlation of little value. A comparison of this small number of cases with figures of American athletes leads one to believe that the vital capacity of the Chinese athlete will differ but little from that of American athletes, when interpreted in terms of surface area. I have not been able to find in the literature any regressions for American athletes, hence I am unable to present a reliable comparison, and my impressions are largely subjective, based on past experience in measuring the vital capacities of American athletes. I hope to present a separate study on this subject later.

It should be borne in mind that in these studies I have been comparing Chinese from a latitude of Georgia and farther south with Americans from a latitude of Nebraska, Ohio and Massachusetts. If there is a marked difference in the vital capacities of Hongkong and Nanking Chinese, there may be a similar difference between Americans of different latitudes as well. The comparisons would, in that case, be more favorable to the Chinese.

All workers in the study of vital capacity have been struck with the relatively large variation in the actual results as compared with the norms. I believe that the possibility of regional variations should be kept in mind. It is natural that with a mixture of types there should be a comparatively large variation from the mean. I have some evidence to show that body type also contributes in some measure to this variation. I have correlated types of build, subjectively judged, with vital capacity, and the shorter, heavier built type has a consistently smaller vital capacity for the same height than does the taller, "rangy" type of build. The correlation I have obtained is small, being 0.238 with less than fifty cases. This may indicate that there is possibly a fruitful field for investigations which may eventually reduce this variability. It may prove that there is a larger variability in nationals of one country, caused by climate, activity and bodily build than is found between nations or races.

SUMMARY

In a study of the vital capacity of Chinese students, the following conclusions were reached:

1. Surface area of the body, computed according to the method of Dubois, offers the criterion which correlates the height with vital capacity.
2. Owing to the curvilinearity of all two-variable correlations, multiple regressions were not reliable.
3. The probable error of the deviations from the "normal" approximated 8.8 per cent of the mean for all ages and 6.8 per cent for college students.

4 Chest expansion gave low correlations with vital capacity when both were corrected for height

5 There is a slight but positive relationship between vital capacity and overweight and underweight

6 Tables are presented for ascertaining vital capacity norms for Chinese students from South China and from East Central China

7 South China students show a larger vital capacity before pubescence and a smaller vital capacity after puberty than is the case for students of East Central China. This is found only for men students, as data for women students of South China were lacking

8 College students of both sexes show a slightly larger vital capacity than do elementary and high school students

9 The vital capacity of Chinese students of East Central China compares favorably with that of American students of both sexes, except that vital capacity of the American college women exceeds that of the Chinese college women to no small degree

10 It is thought probable that there are regional variations in vital capacity which may vary more within one nation than would be the case with similar groups of different races

THE ORAL ADMINISTRATION OF EPINEPHRINE

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As a result of many clinical and experimental investigations, current opinion regards epinephrine as producing little if any effect when administered orally. Sollmann¹ states that "it is entirely ineffective by oral administration" and that "the blood pressure response is practically absent" when given by mouth. In "Useful Drugs"² it is stated that, "when given by mouth, it produces no evident effect on the general circulation." Cushny³ states that "when given by mouth, it has no effect on the blood pressure or heart." According to an article in the "Pharmacology of Useful Drugs,"⁴ "epinephrine is one of the few alkaloids in the materia medica which are not absorbed from the gastrointestinal canal with such rapidity as to induce any appreciable effect." In the recent series of articles on glandular therapy in *The Journal of the American Medical Association*, it was stated,⁵ regarding epinephrine, that "when the drug is administered by mouth, it is quickly destroyed, either by the gastric or by the intestinal secretions, and its systemic effects are consequently not obtained."

ANIMAL EXPERIMENTAL WORK

In experimental work on animals, administration of epinephrine by mouth, except in large doses, does not produce any effect on the blood pressure. Heiter and Wakeman⁶ reported no effects when the drug was given in "ordinary" doses. They found that 10 cc of epinephrine solution (1:1,000) produced no effects in a well fed dog weighing 13 Kg, which they feel corresponds with the known absence of physio-

1 Sollmann, Torald. A Manual of Pharmacology and Its Application to Therapeutics and Toxicology, ed 2, Philadelphia, W B Saunders Company, 1922, pp 385, 387

2 Useful Drugs, Prepared Under the Direction and Supervision of the Council on Pharmacy and Chemistry of the American Medical Association, ed 6, 1923, p 70

3 Cushny, A R. A Textbook of Pharmacology and Therapeutics, or the Action of Drugs in Health and Disease, ed 7, Philadelphia, Lea & Febiger, 1918, p 374

4 Hatcher, R A, and Wilbert, M I. Pharmacology of Useful Drugs, Chicago, American Medical Association, 1915, p 189

5 Wearn, J T. Glandular Therapy. Pharmacology of Epinephrine, J A M A **83** 1508 (Nov 8) 1924

6 Herter, C A, and Wakeman, A J. On Adrenalin Glycosuria and Allied Forms of Experimental Glycosuria Due to the Action of Reducing Substances and Other Poisons on the Cells of the Pancreas, Tr A Am Phys **17** 570, 1902.

logic effect of gland extracts on the human subject. However, with 30 cc of the solution they produced a 1 per cent glycosuria in a dog, over a short period of time, without other symptoms. Falta and Ivocović,⁷ while working on dogs, found that even more than 20 mg a day did not produce any special manifestations. They gave 50 cc of a 1 per cent solution over a period of eleven days, with only a trace of glycosuria on three of the days. Dorlencourt, Trias and Paychère,⁸ giving relatively high doses (0.20 mg per kilogram of body weight in an animal), obtained only hyperglycemia and never any change in blood pressure, from which they concluded that the epinephrine passed through the portal system to the liver, and that none escaped into the general circulation. Rogers⁹ produced a local increase in the size of the thyroid gland by feeding dogs derivatives of the entire suprarenal gland, but he found that feeding with corresponding amounts of epinephrine crystals is without appreciable effect on the thyroid.

CLINICAL OBSERVATIONS

Clinical experiments were carried on by Aschner and Pisk¹⁰ with doses of from 3 to 4 cc of a 0.1 per cent solution in twenty cases. Most of the patients showed a rise in blood pressure, the highest being 86 mm after a dose of 4 cc, this rise usually occurred between five and twenty minutes after administration, in one case, after forty-five minutes. The pulse rate was not constant, being accelerated in some cases and slowed in others. Generalized symptoms of tremor, pallor, excitement and myalgic pains occurred in those cases in which these symptoms followed subcutaneous injection. More often local symptoms of nausea, epigastric and hunger pains were present, and glycosuria was not noted. These authors conclude that orally administered epinephrine in the doses given acts almost exclusively on the blood pressure, the strength of the reaction in the majority of cases running parallel with subcutaneous and intravenous effects. These experiments suggest that epinephrine is absorbed, but in those cases in which only local symptoms were manifest, the rise in blood pressure may have resulted from the local action. The drug was given in solution, and

⁷ Falta, W., and Ivocović, L. Ueber die Wirkungsweise des Adrenalins bei verschiedener Applikation und das Auftreten desselben im Harn, *Wien klin Wchnschr* 22 1780, 1909.

⁸ Dorlencourt, H., Trias, A., and Paychère, A. Stabilisation du faux de la glycémie chez le chien durant le sommeil chlorallosique, *Compt rend Soc de biol* 86 1078 1922, Absorption de l'adrenaline par voie digestive, *ibid* 86 1129, 1922.

⁹ Rogers, J. Adrenal Feeding in Conditions of Hyperthyroidism, *Endocrinology* 6 73 (Jan) 1922.

¹⁰ Aschner, B., and Pisk, H. Ist das Adrenalin vom Magendarmtrakt aus wirksam? *Klin Wchnschr* 3 1265 (July 8) 1924.

while the effect throughout absorption by the mucous membranes of the mouth and pharynx may have been minimal, it cannot be entirely eliminated

As a result of their experimental work with animals, Trias and Doilencourt¹¹ advise the administration of the drug by mouth for the hormonal effect, although it does not cause a rise in blood pressure. They advise giving it in a concentrated solution, the rapidity of absorption being dependent on the concentration. The dose advised varies from five to ten times that of the injection, the doses usually effective and tolerated are from 60 to 100 drops (from 3 to 5 mg). The ingestion of epinephrine sets up a hyperglycemia in proportion to the amount taken. They state that Henri Vignes fully agrees with this method of oral administration basing his opinion on his experience with opotherapy in various gynecologic and obstetric cases.

Biems¹² has made some clinical observations on the effect of epinephrine administered by mouth. He used doses of 4 cc of a 1 per cent solution, and in twenty-one cases observed the effect on the blood pressure and on the blood sugar. In five cases the blood pressure rose, in seven it remained constant, and in the remaining it was lowered. The blood sugar was increased in all cases, and no parallelism was found between the blood pressure and the effects on the blood sugar. The maximum blood pressure in the five cases which showed an increase occurred 15, 30, 60, 60 and 120 minutes after the administration, those showing a fall in blood pressure reached their lowest reading 8, 8, 10, 15, 15, 15, 30, 30 and 90 minutes after the administration. The blood sugar reached its maximum in about an hour.

Weiss and Baitz¹³ did not find any cardiovascular response in ten cases in which they administered 3 mg of epinephrine by mouth, seven cases of which were known to have an acidity. They emphatically disagree with Aschner and Pisk¹⁰ and also with Hepner and Cervenka,¹⁴ who noted a rise in blood pressure with oral administration.

Hitchcock¹⁵ administered epinephrine chloride by mouth in doses of 0.3 cc, 1,000 solution diluted to 100 cc, using the increase in metabolism as the criteria for absorption. In ten of eleven experiments on healthy persons, there was an average rise in metabolism of 6.9 per cent. It is believed that the rise was caused by absorption from the

11 Trias, A., and Dorlencourt, H. How Adrenalin Should Be Given, *J des Practiciens*, Feb 10, 1923, abstr *Practitioner* **110** 333 (April) 1923.

12 Brems, A. Ueber die perorale Adrenalinwirkung, *Acta med Scandinav* **63** 431 (May 27) 1926.

13 Weiss, S., and Baitz, G. Zur Frage der Wirkung des stomachal verabreichten Adrenalins, *Ztschr f d ges exper Med* **49** 543, 1926.

14 Hepner and Cervenka, quoted by Weiss and Baitz (footnote 13).

15 Hitchcock, F. A. The Effect of Ingested Adrenalin Chloride on Basal Metabolism, *Am J Physiol* **69** 271, 1924.

stomach and probably from the upper intestine, and that the extent of the rise indicates the amount of the drug absorbed. These experiments are open to criticism in that again the solution was used, and the effect on the mucous membranes of the mouth and pharynx cannot be eliminated. The ingestion of the amount of fluid used may have caused some rise in the metabolism. The increase in metabolism may have resulted from the local action of the epinephrine on the gastro-intestinal tract through increased peristalsis, with the local symptoms of nausea and distress.

Other writers have mentioned the use of epinephrine by mouth. Harrower¹⁶ cites several instances in which epinephrine by mouth was rapidly effective, and quotes several references regarding this, but none of his facts are convincing. His references indiscriminately include opinion concerning gland extract and epinephrine, and all give the author's opinion rather than definite data. Satterthwaite¹⁷ tried epinephrine by mouth in doses of from 0.6 to 1 cc. of a 1:1,000 solution, but he believes gastric secretions oxidize the active principles before they can reach the circulation, thus depriving them of physiologic properties. Milian¹⁸ recommends epinephrine in 2 mg. doses in water by mouth before the administration of arsphenamine, the dose being repeated five minutes before injection and again an hour afterward. He also gives 1 mg. by mouth morning and evening on the four days following the injection. Signs that the patient is under the influence of epinephrine are: blanching of the face, rise in arterial pressure, tachycardia and generalized tremor.

Hoxie and Morris¹⁹ report a case of asthma of six years' duration. They say: "It is interesting to note that the use of adrenalin even by mouth gave some relief," although mention is not made of the type of the preparation used or any objective data concerning the effect. Alvarado and Arroyabe²⁰ have found epinephrine administered orally efficacious in arresting vomiting in malaria.

ACTION ON GASTRO-INTESTINAL TRACT

There is a great deal of discrepancy in opinions regarding the effect of epinephrine on the stomach and intestine. Much of the work which has been reported has been done on experimental animals and so does

16 Harrower, H. R. Oral Administration of Adrenalin, *New York M. J.* **104**: 893 (Nov. 4) 1916.

17 Satterthwaite, T. E. Drug Therapy in Cardiovascular Diseases, *Internat. Clin.* **1**: 26, 1916.

18 Milian, G. L'administration de l'adrenaline, *Paris med.* **8**: 81 (Feb. 2) 1918.

19 Hoxie, G. H. and Morris, H. T. Adrenalin in Asthma. A Case of Chronic Adrenalism, *Endocrinology* **4**: 47, 1920.

20 Alvarado, R. and Arroyabe, V. Treatment of Vomiting in Malaria, *Prensa med. argent.* **13**: 242, 1926, abstr., *J. A. M. A.* **87**: 1690 (Nov. 13) 1926.

not necessarily apply to man, and the difference in effect between local application and perfusion is not clear. Heinekamp²¹ summarizes the opinion of eighteen reports in which inhibition of peristalsis was the chief observation and seven others in which increased peristalsis was noted. Summarizing, he states in general that the work to date, most of which has been done on excised tissue from the rabbit or frog, indicates (1) that epinephrine ordinarily relaxes the gastro-intestinal canal with the exception of the sphincters, which are contracted, and (2) that epinephrine in minute quantities causes contraction of the intestine. The conclusions to his own work state that epinephrine in minute doses stimulates the peripheral vagus apparatus. The vagus threshold is normally lower to epinephrine, but the maximal effect is so much less than that of the sympathetic nerves that the action of the latter predominates unless small amounts of epinephrine are used. The effect in man is difficult to interpret in view of these conclusions. Epigastric pains following the oral administration, which may or may not be due to contractions of the stomach, have been noted repeatedly in this series and have also been noted by Biems,¹² and by Aschner and Pisk.¹⁰ Tenesmus was present in seventeen of thirty-one cases after rectal administration,^{21a} this is also reported by Muirhead.²²

The statement of Daniélopou²³ referred to, that epinephrine frequently increases the contractility of the stomach, is based on observations made by him in which the stomach was observed by fluoroscopy following the administration of epinephrine by mouth. Strong contractions of the musculature of the stomach were observed, on which grounds the writers referred to feel that epinephrine is contraindicated in treatment for hemorrhage from gastric ulcer. Katsch,²⁴ in 1913, using the roentgen ray, found that epinephrine effected motor inhibition of the gastro-intestinal tract. Dickson and Wilson²⁵ watched the effect of various drugs on the motility of the stomach under fluoroscopy following a barium meal. Epinephrine, in 0.5 cc of a 1 per cent solution, given subcutaneously, inhibited peristalsis of the stomach for two minutes in the first three cases investigated, but did not have an appreci-

21 Heinekamp, W. J. R. The Splanchnic Action of Adrenalin on the Intestines, *J. Lab. & Clin. Med.* **11** 1062 (Aug.) 1926.

21a Menninger, W. C., and Heim, H. S. The Rectal Administration of Epinephrine, *Am. J. Med. Sc.* **172** 425 (Sept.) 1926.

22 Muirhead, A. L. An Autograph History of a Case of Addison's Disease, *J. A. M. A.* **76** 651 (March 5) 1921.

23 Daniélopou, D. Substances Acting on the Vegetative Nervous System, *Paris méd.* **33** 657 (May 20) 1925.

24 Katsch. *Fortschr. a. d. Geb. d. Röntgenstrahlen* **21** 159, 1913.

25 Dickson, W. H., and Wilson, M. J. The Control of the Motility of the Human Stomach by Drugs and Other Means, *J. Pharmacol. & Exper. Therap.* **24** 33, 1924-1925.

able effect in the next seven. In one case there was an apparent increase in depth of the peristaltic contractions. Precaution was taken to use freshly prepared epinephrine, and the authors suggest that the discrepancies were due to variations in the rate of absorption. Intravenous administration was not employed.

In two cases in the present study, 4 mg of epinephrine in a capsule was given by mouth, and the stomach was observed under the fluoroscope following a barium meal. The blood pressure did not vary in either case, and there was no apparent alteration from the normal gastric peristalsis in either case.

It is of interest to note that although Daniélopou and Carniol²⁶ strongly advised against the use of epinephrine for hemorrhage in gastric ulcer, the method of therapy was suggested twenty-five years previously and has been extensively used since that time. It was originally suggested by Grunbaum²⁷ in 1900, who recommended one or two crushed 5 grain (0.324 Gm) tablets of the suprarenal extract. Falta and Turin²⁸ have used as high as 7 mg of epinephrine by mouth, three times a day, as a method of controlling gastric hemorrhage, and they have obtained good results. On this point, Wiggers²⁹ concluded from his studies on the effect of epinephrine on intestinal hemorrhage that large doses were always contraindicated, but in cases in which bleeding has been profuse and a low blood pressure already exists, small doses (from 0.01 to 0.025 mg) administered by continuous intravenous injection are therapeutically desirable.

EFFECT ON GASTRIC SECRETIONS

The effect on gastric secretion of epinephrine orally administered has received considerable attention, as well as the effect of gastric secretions on epinephrine. Yukawa³⁰ studied the effect of the ingestion of epinephrine in fifty cases; in forty-seven, he observed the increase of the secretion of hydrochloric acid. In experimental work on dogs he was able to show that oral as well as intravenous administration was followed by augmentation in the gastric secretion. Loeper and Verpy³¹

26 Daniélopou, D., and Carniol, A. Action de l'adrénaline sur l'estomac de l'homme. Voie intraveineuse et voie gastrique, *Compt rend Soc de biol* **87** 716, 1922.

27 Grünbaum O. F. F. Suprarenal Gland Extract as a Hemostatic, *Brit M J* **2** 1307, 1900.

28 Falta and Turin. In Falta, W. *Endocrine Diseases*, trans by M. K. Meyers, ed 3, Philadelphia, P. Blakiston's Son & Company, 1923, p. 361.

29 Wiggers, C. J. The Effect of Adrenalin on Intestinal Hemorrhage, *Arch Int Med* **3** 139 (March) 1909.

30 Yukawa. Klinischexperimentelle Untersuchungen der Adrenalin Wirkung auf die Magendrüsens. *Arch f Verdauungskr* **14** 166, 1908.

31 Loeper and Verpy. L'action de l'adrénaline sur le tractus digestif, *Soc de Biol* July 28, 1917, quoted by Hernando. *Presse med* **31** 797 (Sept 19) 1923.

were able to demonstrate an increase in the secretion of gastric juice, particularly of free hydrochloric acid, in man following administration of epinephrine by intramuscular injection Binet³² observed the increase in gastric secretion as well as an increase in the amount of hydrochloric acid. The maximal amount is reached in an hour, and decreases after an hour and thirty minutes.

In contrast to these observations, Rogers, Rahe and Ablahadian³³ produced an inhibition or at least a diminution of gastric juice following intravenous injection. Boenheim³⁴ usually obtained a decrease in the free acidity, although sometimes an increase in the quantity of the gastric secretion occurred. In experimental work on dogs, Hess and Gundlach³⁵ found that epinephrine always diminished the total quantity of gastric juice as well as the concentration of hydrochloric acid.

The work of Hernando³⁶ somewhat explains these divergent results. In nine cases in which he administered epinephrine by mouth, six showed an increase in the free and the total acid, and in the others it remained either constant or diminished. An intravenous injection of 0.25 mg was usually followed by an increase, although a dose of 0.05 mg caused a diminution. Amounts of the drug between these doses gave varying results. The effect here may result because small doses stimulate the peripheral vagus apparatus, but the maximal effect of this system is so much less than that of the sympathetic nerves that the action of the latter predominates unless small amounts of the drug are used. The author interprets the effect of epinephrine when administered by mouth as a consequence of the local action of the drug, or its derivative, on the glands of the stomach.

The effect of gastric secretion on epinephrine is variously described. The drug is a weak base, its salts oxidize readily and are rapidly destroyed by strong acids and weak alkalis³⁷. Lesne³⁸ found that epinephrine is not destroyed by pepsin or pancreatin, although profusion

32 Binet, L. L'action de l'adrenalin sur le tube gastro-intestinal, *Presse méd* **26** 407, 1918.

33 Rogers, J., Rahe, J. M., and Ablahadian, E. The Stimulation and Inhibition of the Gastric Secretion Which Follows the Subcutaneous Administration of Certain Organ Extracts, *Am J Physiol* **48** 79, 1919.

34 Boenheim. Ueber den Einfluss von Blutdrüsen-Extrakten auf die Magen-sekretion, *Arch f Verdauungskr* **26** 74, 1920.

35 Hess and Gundlach. Der Einfluss des Adrenalins auf die Sekretion des Magensaftes, *Arch f d ges Physiol* **185** 122, 1920.

36 Hernando, T. Action de quelques médicaments sur la secretion gastrique, *Presse méd* **31** 797 (Sept 19) 1923.

37 Moore, B., quoted from Sollman, 1895, p. 335. Wearn (footnote 5), Satterthwaite (footnote 17).

38 Lesne, E. De l'administration de l'adrenaline par le voie digestive, *Bull et mém Soc méd d hôp de Paris* **44** 800, 1920.

of the liver deprives it of its toxicity either partially or entirely ³⁹ Binet ³² notes that it is not altered by pepsin, trypsin or by passage through intestinal capillaries Daniélopou ²³ explains the increase in contractility of the stomach on the administration of epinephrine by the fact that a large part of the drug is oxidized by the gastric juice, "while the intact small remnant may exert an action on the parasympathetic"

In summarizing the reports given in the literature, one is impressed by the diversity of opinion, as well as by the contrasting experimental and clinical observations

The literature at hand shows that in some cases the pharmacologic effect of epinephrine on the stomach may stimulate peristalsis, while in other instances it inhibits this action The paradox is probably explained by the fact that the vagus system is stimulated by small doses, and when this maximal effect is produced, peristalsis results It is probably the same mechanism that operates in the case of gastric secretion

Despite the simplicity of the explanation and its apparent validity as applied to the pharmacodynamics of epinephrine on the musculature of the stomach, it does not explain the variance in clinical results obtained in the oral administration of the drug There is a marked contrast between the results obtained in oral administration even by observers who have conducted special investigations in this field

PRESENT STUDY

The method used in the present series has been the same in all cases The patient is kept resting in bed for at least twelve hours preceding the observation if possible Several control blood pressures and pulse readings are made before the drug is administered Epinephrine in doses varying from 2 to 6 mm is administered in a gelatin capsule on an empty stomach, after which blood pressure and pulse readings are made at frequent intervals over a period of at least an hour and as long as five hours if necessary In most of the cases determinations of the basal metabolism were made, either previous or subsequent to the administration of the epinephrine Twenty-eight observations have been made on twenty-one patients, sixteen of the cases were various forms of hyperthyroidism, there was some suggestion of hypothyroidism in four of the remaining cases It is purely speculation as to whether the condition of the thyroid function had any effect on the clinical manifestations of the drug, but in view of many reports of epinephrine sensitization in hyperthyroidism, it is my opinion that there is a definite, although ill defined, relationship

³⁹ Gioffredi, C La distruzione dell'adrenalina nell'organismo, Arch di farmacol sper 6 607, 1907

The cases in this series can be divided into four groups according to the blood pressure effects. Decrease in blood pressure of from 2 to 10 mm, nine cases, no change in blood pressure, six cases, increase in blood pressure of from 5 to 15 mm, six cases, increase in blood pressure of from 15 mm and over, seven cases. Besides the nine cases which showed a fall in blood pressure, there were other cases which showed a slight fall at some stage in the observations, but in which the predominating change was a rise.

In none of these cases was the fall in the blood pressure sufficient to warrant inference that it might be due to the drug. The enforced rest probably adequately explains the change. The second group of six cases in which there was no change either in a rise or fall of the blood pressure, does not require special comment. In the six cases in which there was a rise of from 5 to 15 mm, the increase probably is explained on the basis of a slight emotional or physical restlessness during the course of the observation. Only two of the patients in these cases might be exceptions to this—one voluntarily mentioned some abdominal distress, and the other noted an increase in the tremor of the hands.

In the seven cases presenting a rise in blood pressure of 15 mm and over, the rise in the systolic pressure was as follows: 16, 18, 20, 28, 30, 50 and 110 mm. The rise in diastolic pressure in all cases was approximately proportionate to that of the systolic, but usually was not as great. The pulse rate varies, in some cases it increases in proportion to the rise in blood pressure, while in other cases it does not change even though there is considerable change in the blood pressure. In these cases the duration of the rise in blood pressure varies, but in every case the duration is particularly noteworthy. In contrast to the duration of the effects of intravenous or intramuscular administration of the drug, the shortest duration of the increased blood pressure in any of these cases is thirty-five minutes. A second was thirty-six minutes, one lasted forty-eight minutes, two approximately sixty minutes and two approximately ninety minutes.

While the results in different cases show some variation, the data are given in three cases for illustration.

CASE 1—W. W., a man, aged 45, who had been admitted to the hospital before, once with the diagnosis of chronic interstitial nephritis and the second time with the diagnosis of chronic valvular disease, had had exophthalmos and goiter for about three years.

When admitted to the hospital, he had marked tremor, dyspnea and enlarged heart and vomited. The basal metabolism was plus 52.2. The blood pressure was 197 systolic and 112 diastolic.

Chart 1 graphically sets forth the table of data. On the day following the observation, the patient subjectively felt better than at any time previously during his stay in the hospital. The pulse rate was 74, the lowest while the patient was in the hospital.

TABLE 1—*Observations Made Five Days Subsequent to Ligation of Inferior Thyroid Artery in Case 1*

Time	Time Interval (Minutes)	Pulse	Blood Pressure		Comment
			Systolic	Diastolic	
8 45		80	184	98	
8 48		82	184	96	
8 54		78	178	94	
8 55	Epinephrine 3 mg tablets in gelatin capsule by mouth				
8 57	3	80	182	94	
9 00	5	80	178	90	
9 03	8	84	182	94	
9 05	10	80	176	96	
9 08	13	78	174	94	
9 13	18	84	212	104	Nausea
9 16	21	80	234	112	Abdominal "cramps"
9 19	24				Vomited
9 21	26	100	270	120	
9 30	35	132	290	160	
9 32	37				Glyceryl trinitrate, 1/50 grain (0.001 Gm)
9 35	40	112	285	150	Severe precordial pain
9 39	44	104	268	134	
9 41	46				Vomited
9 44	49	96	254	140	
9 48	53	96	236	134	Marked tremor of hands
9 53	58	96	234	132	Sweating, severe pain
9 58	63	96	228	126	
10 05	70	90	204	116	
10 10	75	90	192	110	
10 15	80	90	186	100	
10 20	85	88	182	100	
10 25	90	86	180	100	
10 30	95	88	178	98	
10 45	110	80	176	90	
2 00	300	80	182	96	

TABLE 2—*Observations Made in Case 2*

Time	Time Interval (Minutes)	Pulse	Blood Pressure		Comment
			Systolic	Diastolic	
8 12		134			
8 14		132	136	60	
8 16		132	136	58	
8 18	4 mg epinephrine in capsule by mouth				
8 20	2	130	134	58	
8 25	7	126	132	58	
8 29	11	132	130	58	
8 31	13	130	138	64	
8 35	17	130	136	60	
8 38	20	126	132	58	
8 41	23	128	144	70	Belching, "pain in stomach"
8 44	26	130	164	76	Nausea
8 49	31	131	166	80	Sweating
8 51	33	134	186	90	Vomiting
8 52	34	134	186	84	Less pain—"cramps"
8 53	35		164	74	
8 55	37	128	158	74	Headache (no tremor)
8 58	40	130	150	70	
9 01	43	126	146	70	Slight epigastric pain
9 04	46	126	138	64	
9 05	49	128	138	62	No subjective symptoms remaining
9 13	55	126	136	62	
9 18	60	126	136	62	

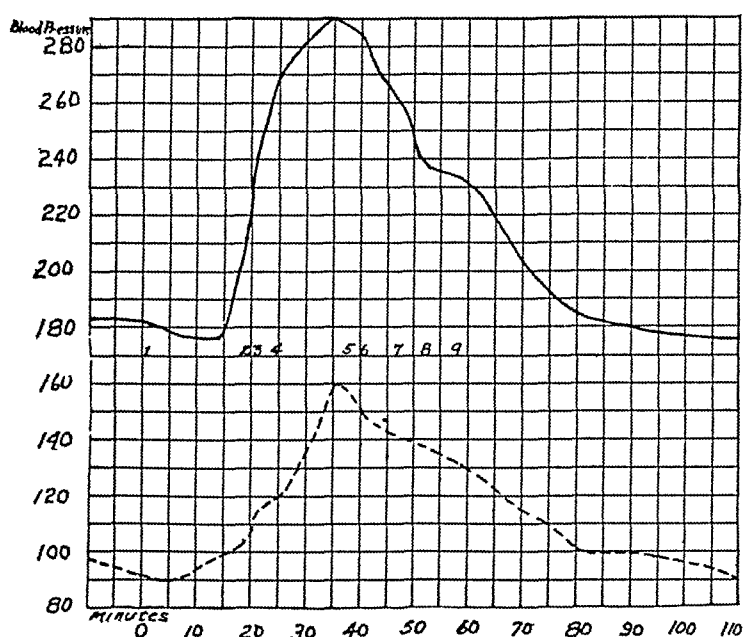


Chart 1 (case 1) —Effect of 3 mg of epinephrine on the blood pressure when administered by mouth in a capsule. In these charts, the solid line indicates systolic blood pressure, the dotted line, diastolic. 1, epinephrine administered, 2, vomited, 3, "cramps" began, 4, vomited, 5, spirit of glyceryl trinitrate, 6, vomited, 7, precordial pain most severe, 8, marked tremor and 9, sweating

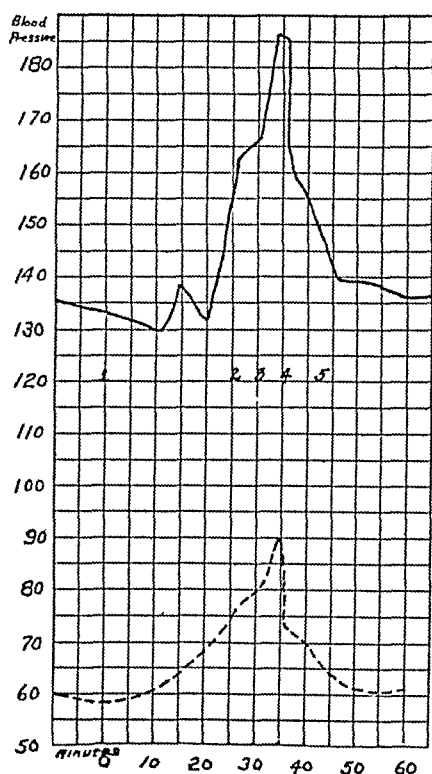


Chart 2 (case 2) —Effect of 4 mg of epinephrine on the blood pressure when administered by mouth in a capsule. 1, epinephrine administered, 2, nausea, 3, sweating, 4, vomiting and 5, slight epigastric pain

CASE 2—I N, a woman, aged 30, had had exophthalmos, a moderately enlarged heart and a slight tremor for one year. The basal metabolism was reported as plus 90, but was not rechecked. On the previous day, 2 mg of epinephrine had not produced any effect.

CASE 3—J F, a man, aged 43, had been troubled with symptoms of hyperthyroidism for four years: goiter, exophthalmos, tachycardia and tremor. He had been operated on about three years previously, but had not obtained relief. The inferior thyroid arteries were ligated on Jan 23, 1925. The basal metabolism on Feb 17, 1925, was plus 60.

In the total series, certain systemic effects from the drug other than changes in the blood pressure were noted as shown in table 4.

The most frequent symptom, abdominal distress, varied in character from severe abdominal cramps to only a sensation of burning. In one

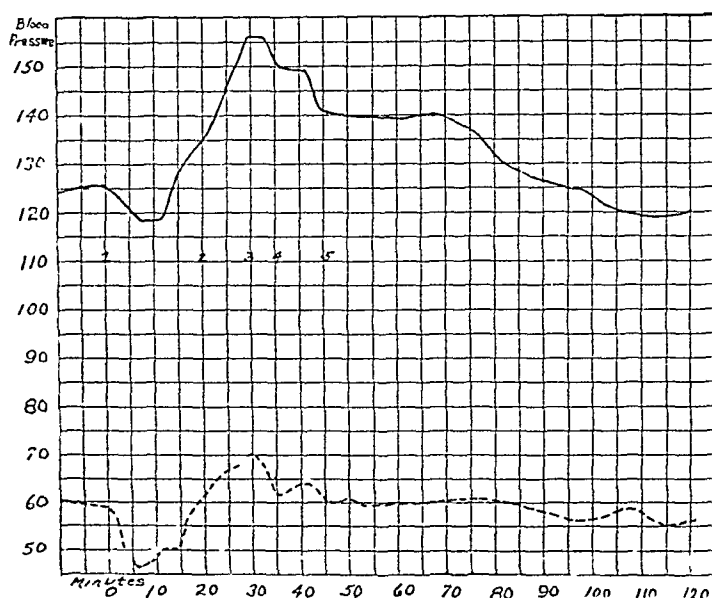


Chart 3 (case 3)—Effect of 3 mg of epinephrine on the blood pressure when administered by mouth in a capsule. 1, epinephrine administered, 2, "burning" sensation in epigastrium, 3, nauseated, 4, "choking" sensation and 5, no subjective sensation remains.

case the patient described the sensation as that of weight. In seventeen cases in which the basal metabolism was recorded, there was no apparent relationship between the basal metabolism and the effect of the drug by this method of administration. Various types of cases of hyperthyroidism with approximately equal metabolic rates do not give the same effect with oral administration. In two cases larger doses produced slightly more marked effects, while in three other cases an increase in the amount of the drug on the second observation did not produce further effects.

The interpretation of these results is difficult, if not impossible, from the knowledge now at hand. On the assumption that the vagus system is stimulated by smaller doses and the sympathetic system by larger

doses, it would be expected that in cases in which a small dose is effective in producing abdominal distress, a larger dose should give no response. However, as has been noted, the response was greater with an increased dose in two cases. Peristalsis has occurred in this series, as well as in

TABLE 3—*Observations Made in Case 3^a*

Time	Time Interval (Minutes)	Pulse	Blood Pressure		Comment
			Systolic	Diastolic	
8 57		96	125	60	Systolic sound distinct, diastolic poorly defined, fades away
9 00		96	127	58	
9 04		95	126	58	Supper at 5 30
9 07	3 mg epinephrine in capsule by mouth				
9 09	2	96	120	48	"Burning" sensation in epigastrium, sense of pressure or weight in epigastrium, not nauseated
9 14	7	94	118	46	
9 18	11	94	118	50	
9 21	14	94	128	50	
9 23	16	94	130	56	
9 25	18	91	134	60	
9 27	20	98	136	60	
9 29	22	98	142	64	
9 31	24	98	145	64	
9 34	27	98	150	68	
9 36	29	98	156	70	Nauseated, no acute distress
9 39	32	100	156	63	"Burns" under sternum
9 42	35	98	150	62	"Choking" sensation, respiration slightly increased
9 44	37	94	148	64	No sensation remains
9 47	40	94	148	64	
9 51	44	94	142	60	
9 56	49	94	142	62	
9 59	52	96	136	60	Changed position in bed
10 03	56	94	138	60	
10 05	58	94	136	60	
10 09	62	94	138	60	
10 14	67	94	140	60	
10 20	73	94	138	62	
10 23	76	94	136	56	
10 27	80	92	132	58	
10 34	87	92	130	58	
10 44	97	92	124	56	
10 49	102	92	122	58	
11 02	115	90	118	55	
11 07	120	90	120	56	

^a Patient has occasional extrasystoles at this point, single beats came through (systolic pressure) as high as 168 mm.

* A repetition of this observation five months later after the administration of 4 mg of epinephrine did not produce any effect. The patient's basal metabolism at that time was plus 10.

TABLE 4—*Symptoms Manifested After Administration of Epinephrine*

Abdominal distress	6 cases
Substernal distress	4 cases
Respiratory distress	4 cases
Nausea	3 cases
Tremor	3 cases
Sweating	2 cases
Vomiting	2 cases
Headache	1 case
Dryness of the mouth	1 case

the series of rectal administration, with sufficient frequency to leave no doubt concerning the stimulation of the vagus system on those occasions. The absence of peristalsis does not signify a stimulation of the sympathetic system, although such may be the case. The effect that the various

gastric and duodenal secretions may have on the drug is also difficult, if not impossible, to state. In those cases in which peristalsis resulted there probably was also a stimulation of secretory activity which at least theoretically should have destroyed the drug. In cases in which peristalsis was not apparent, the secretory activity may have been inhibited, it certainly was not stimulated, consequently in the absence of secretion, destruction of the drug would be delayed, and the systemic effects would be more marked, however, this was not observed.

The effects on the blood pressure may be a secondary result of the drug. The local effect in the stomach was to produce peristalsis and general distress. The abdominal cramps associated with the patient's consequent tenseness may, to some degree, explain the rise in blood pressure. To be certain that it was due to absorption would be necessary in order to test the blood for the presence of epinephrine, this was not done. However, in the presence of other systemic manifestations such as dryness of the mouth, increase in the tremor or respiratory distress, it seems probable that the effect on the blood pressure was primarily the result of the drug in the blood stream.

The vasoconstricting quality of the drug makes it unlikely that its administration by mouth will be effective. Undoubtedly, it is destroyed in the presence of strong acids and even of weak alkalis, consequently, when they are present in the stomach in sufficient quantity, the drug will be destroyed before it can be effective. From these experiments, it seems unlikely that it would be of any value and certainly might be of considerable harm in gastric hemorrhage. There is not sufficient evidence to show that the oral administration is effective in small doses, such as are often recommended, and in larger doses its effectiveness is so inconstant and unreliable that administration by this method is not to be commended.

CONCLUSIONS

- 1 The oral administration of epinephrine is inconstant and unreliable, and for this reason it cannot be satisfactorily used for therapeutic purposes or for any form of sensitization tests.

- 2 The oral administration of the drug in man produces effects which have not as yet been explained in the light of animal experimentation.

- 3 Despite the generally expressed opinion to the contrary, epinephrine is absorbed in the gastro-intestinal tract (other than the mouth and throat) in certain cases as evidenced by changes in blood pressure, increased tremor, sweating, abdominal distress and other systemic manifestations of the drug.

PERICARDIAL PAIN

AN EXPERIMENTAL AND CLINICAL STUDY *

JOSEPH A CAPPS, M D

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In a perusal of the literature one encounters diverse opinions concerning the rôle of pain in pericarditis

Strumpell ¹ says

Pain may be felt in the cardiac region and often in the epigastrium, but is absent in many cases. Dyspnea and pectoral distress are almost constant

Hirschfelder,² considers that "In simple fibrinous pericarditis, precordial pain is the most striking symptom"

Musser,³ says

Pain is frequently present, it may be lancinating, dull or heavy, localized in the fourth and fifth spaces or referred like angina pectoris, but modified by pressure

Pick and Hecht ⁴ write

Pericarditis usually causes discomfort which is localized in the region of the heart and is described as pressure. Pronounced pain may be present radiating to the arms and shoulders. Epigastric pains have also been observed

Norris and Landis ⁵ assert

Pain may be entirely absent or may be of a very sharp, stabbing character. Usually it is felt over the heart, but it may radiate into the abdomen, to the left side of the neck or shoulder. Often it is increased by movement, deep breath or cough. Tenderness may be elicited by pressure in the region of the apex. Also there may be a feeling of oppression or tension in the precordium

Mackenzie,⁶ on the other hand, says

Dry pericarditis is essentially a painless complaint. This curious painlessness has long puzzled me. When pains are associated with pericarditis it will invariably be found that there is evidence of myocardial affection

* Read before the Association of American Physicians, May 3, 1927

1 Strumpell. Text Book of Medicine, 1893

2 Hirschfelder, A. D. Diseases of Heart and Aorta, Philadelphia, J. B. Lippincott Company, 1910

3 Musser, J. H. Medical Diagnosis, Philadelphia, Lee and Febiger, 1913

4 Pick and Hecht. Clinical Symptomatology, New York, D. Appleton & Company, 1911

5 Norris and Landis. Diseases of the Chest, Philadelphia, W. B. Saunders & Company, 1918

6 Mackenzie, J. Diseases of the Heart, New York, Oxford University Press, 1908

It is of interest to note that many years before Head,⁷ found that "Pericardial pain like that of pleurisy is local, with more or less deep tenderness" He thought the pain was never referred

Levine⁸ refers to "precordial pain as the most characteristic complaint in pericarditis and in rheumatic patients a very common one" He quotes Sibson as having found pain present in 70 per cent of his series "The pain is apt to be sharp, stabbing, aggravated by cough and deep breathing and may extend to the shoulder, arm, neck or abdomen In older people and in nephritics pain need not be present"

A graphic description of acute pericarditis is given by Allbutt⁹

There may be neither symptom nor sign Usually the patient complains of a dull, wearisome ache rather than an acute pain In other cases the distress varies from slight discomfort to a severer pain aggravated by movement, deep inspiration or cough It may be seated in the epigastrium or reflected towards the neck and shoulder blade and shoulder Finally the pain may be retrosternal, especially in the angino-form attacks If the phrenic nerve be engaged, two tender points may be observed, one over the sterno mastoid muscle, the other at the xiphoid Not infrequently there is pain on swallowing

To reconcile these seemingly conflicting statements it is obvious that one should have more accurate knowledge of the exact location of the inflammatory process responsible for each clinical pain picture described

A simple pericarditis involves only the serous layers of the pericardial sac According to Allbutt, the inflammation may extend upward involving the sheath of the aorta and thereby produce symptoms of angina

The fibrous pericardium is in contact anteriorly and posteriorly with the pleural membranes, while laterally it is in close contact with the mediastinal portion of the parietal pleura The base of the pericardium is attached to the central tendon and to the adjacent part of the muscular substance of the diaphragm As a result of these close relationships, it is apparent that extension of a serous pericarditis through the fibrous sac may set up pleuropericarditis in different localities Conversely, it is a common event for an inflammation of the anterior or posterior mediastinum or of the diaphragmatic pleura to extend inward to the serous pericardial sac

When one considers that pericarditis may be confined to the serous lining alone, or be associated with inflammation of the fibrous layer or of the adjacent costal and diaphragmatic pleura, it is not surprising that the pain phenomena are variable

The purpose of this study is to determine, as far as possible, what structures within and adjacent to the pericardium are capable of producing pain and what laws govern the distribution of this pain

7 Head, H Brain **19** 153, 1896

8 Levine Nelson's Loose Leaf Medicine **4** 182, 1920

9 Allbutt, C Oxford System of Medicine **2** 261, 1920

The most reliable evidence bearing on this question is to be obtained by direct incision of the various structures within and around the pericardial sac and the careful recording of painful sensations thereby induced, both with respect to quality and localization. Such observations, of course, cannot be made on animals, and only exceptionally does the opportunity present itself in man. In the presence of a large pericardial effusion which displaces the lung, I have found conditions favorable to the making of pain tests during the therapeutic drainage of the fluid.

After careful orientation of the pericardial border by means of percussion and the roentgen ray, the skin is anesthetized with ethyl chloride and a trocar inserted not far laterally from the left border. The first thrust through the parietal pleura is always accompanied by the characteristic local pain. This is allowed to subside before the second thrust is made through the pericardial membrane. The presence or absence of pain from this penetration is noted. Before withdrawing much fluid a silver wire is introduced through the hollow cannula and the heart and serous walls stimulated by pressure of the point and by scratching movements, as extensively as possible. By making every movement deliberate and by assurance of the patient, this can be performed with little discomfort and with cooperation.

The clinical study of pericardial pain is made difficult by the frequent association of pericarditis with disease of the heart and with disease of the nearby lungs and pleurae. In order to reduce the problem to the simplest terms, I have chosen only the less complicated cases for study. I have purposely avoided cases of the pericarditis complicating pneumonia, tuberculosis and aneurism because of the increased difficulties of interpretation. Whenever possible the exact nature and location of the lesion has been confirmed by roentgen-ray examination and necropsy.

For convenience, my observations have been divided into the following groups:

1 Experimental Results

Pain caused in penetrating the pericardial sac and the sensation produced by exploration of the parietal and visceral portions of the serous layer with a silver wire were noted in tapping pericardial effusion.

2 Clinical Observations

- (a) Acute and subacute pericardial effusions
- (b) Dry pericarditis
- (c) Dry pericarditis following coronary thrombosis
- (d) Pleuropericarditis

EXPERIMENTAL RESULTS

CASE 1—R. J. had had tuberculous pericarditis of several weeks' duration, accompanied by a large bloody effusion. Paracentesis was performed with a trocar in the fourth left interspace, well outside the mammary line. As the

parietal pleura was pierced there was the well known, sharp, localized pain. Pain was not experienced as the pericardium was entered either over the heart or elsewhere. A silver wire was introduced through the hollow cannula. Contact with and scratching of heart and parietal pericardium did not cause pain. A second tapping in the same locality a week later gave identical results (fig 1).

CASE 2—J. N. had had chronic tuberculous pericarditis with large effusion. Paracentesis was performed in the fourth left interspace outside the mammary line. Piercing the pericardial sac or pressure of wire on the heart and on the serous covering of the sac wall did not cause pain. When the wire passed under the apex and produced a "tripping," the patient complained of a "queer aching" sensation over the area of the heart "like pressure."

CASE 3—T. W. had subacute rheumatic pericarditis with large effusion. Paracentesis was performed in the fifth left interspace lateral to the mammary line. As the trocar pierced the pericardium the patient complained of a sharp pain in the midtrapezius ridge, a pain in marked contrast to the local pain expe-

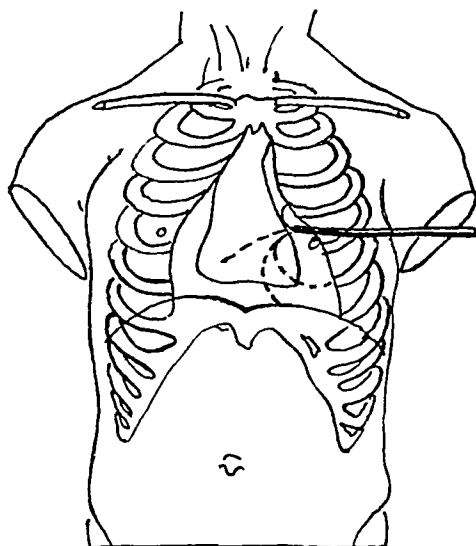


Fig 1 (case 1) —Showing the method of exploration in a case of pericardial effusion. Paracentesis of the pericardium at the fourth space, irritation of the serous pericardium and irritation of the heart did not produce pain. Second paracentesis in the fourth space gave similar results.

rienced when the parietal pleura was punctured. Pressure and scratching of the tip of the silver wire over the surface of the heart and the inner pericardial wall did not cause pain.

A second paracentesis in the sixth left interspace outside the mammary line also caused pain in the neck in the same area as in case 3. Exploration of the inner sac again did not cause a sensation of pain (fig 2).

CASE 4—A. E. had subacute rheumatic pericarditis with effusion. Paracentesis was performed in the fifth left interspace outside the left mammary line. Piercing the wall of the chest and parietal pleura caused local pain. Piercing the pericardium gave rise to a sharp, lancinating pain over the outer third of the trapezius ridge. Pressure of the wire point and a scratching movement over the heart and over the posterior and lateral portions of the inner wall did not cause pain. "Tripping" the heart apex with the wire produced skipped beats and an "uncomfortable feeling" over the heart, but without pain.

COMMENT

It will be noted that in three instances in which the pericardium was punctured at the level of the fourth interspace pain was not experienced, while in the two punctures at the level of the fifth space and one at the sixth space, pain was felt in the neck

From previous experiments carried out by the wire method, it is known that irritation of the pleura covering the diaphragm from the pericardial junction to a short distance from the costal attachment also gives rise to pain in the neck. One may reasonably conclude that afferent fibers of the phrenic nerve supply the central portion of the diaphragm and extend upward to a distance of from 1 to 2 inches (2.5 to 5 cm) over the surface of the fibrous pericardium (fig 3)

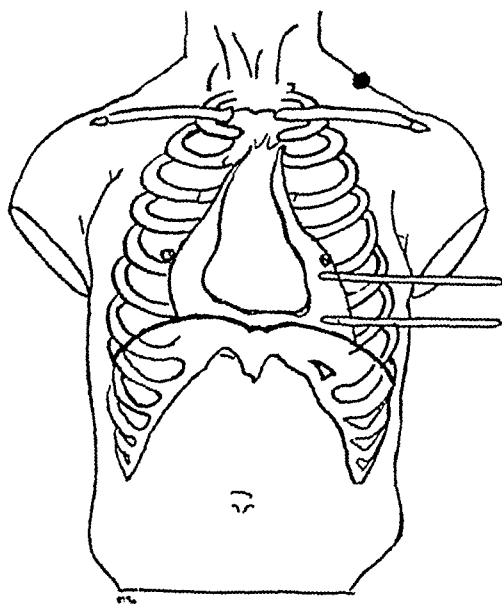


Fig 2 (case 3) —Showing the results of exploration in a case of pericardial effusion. Paracentesis of the pericardium in the fifth space and paracentesis in the sixth space produced pain in right trapezius region. Irritation of the serous pericardium and irritation of the heart did not produce pain.

The irritation from the wire of the serous pericardium overlying the heart seems to demonstrate that this area is insensitive to pain, but as it was impossible to explore the investing sheath of the aorta and pulmonary artery, one should not assume that the sense of pain is absent. The lateral walls of the serous pericardium were irritated by the wire at many points, always with negative results. The base of the pericardial sac could not always be satisfactorily explored on account of the impeding motion of the left side of the heart, but all attempts to elicit pain in this area were fruitless.

CLINICAL OBSERVATIONS

(A) *Chronic Pericardial Effusion*—The following are illustrative cases

CASE 1—R J had chronic tuberculous pericarditis with large effusion. The patient was not seen when the condition was in the acute stage. Friction sounds were not heard over the heart or lungs. Orthopnea, dyspnea and distress and oppression over the region of the heart were experienced. Sharp pain did not occur over the heart or in the chest, neck or shoulder.

CASE 2—C T had chronic pericarditis with large effusion, probably tuberculous. Dyspnea and orthopnea were present. Deep pressure over the heart did not cause tenderness. There was no pain over the heart, chest, neck or shoulder. While under observation during the subsidence of the effusion, a to-and-fro friction appeared for two or three days, but was not associated with pain.

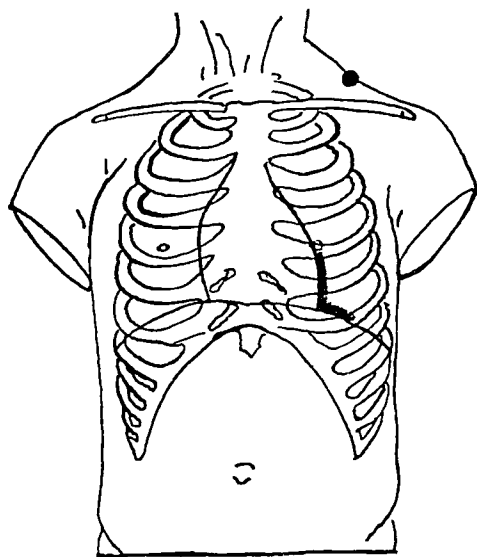


Fig 3—Shading shows portion of fibrous pericardium and central diaphragm, irritation of which gives rise to neck pain

CASE 3—A E had had rheumatic pericarditis with effusion of two weeks' duration. A sense of precordial tightness and oppression was felt, but there was no pain over the heart, chest or neck. Pressure over the heart did not cause tenderness. On the fourth day of observation, a distinct to-and-fro friction was audible over the base, continuing for several days, but without pain.

CASE 4—J N had chronic tuberculous pericarditis with effusion. Dyspnea and a tight feeling over the sternal region were experienced. Pain was not felt over the heart, chest, neck or shoulder. Pressure over the precordium did not cause tenderness.

(B) *Dry Pericarditis*—The following are illustrative cases

CASE 1—L L had fibrinous pericarditis developing as a late complication in a case of septicemia. There was also hemolytic streptococcus infection with gangrene of the leg. Thirty-six hours before death the patient developed a distinct to-and-fro friction over the apex of the heart. Although his mind was clear he did not feel pain or distress over the heart or tenderness to

deep pressure At postmortem examination, a patch of fresh fibrinous exudate was found over the left ventricle and apex Pleurisy was not present

CASE 2—A C had dry pericarditis and terminal endocarditis A loud friction rub was heard over the whole area of the heart A grating sensation could be felt with the hand There was a slight rise of temperature Distress or pain of any kind was not felt over the heart, chest or neck Deep pressure did not elicit tenderness At necropsy two days later, a rich fibrinous exudate was found covering the heart and the complete serous lining of the sac The patient did not have pleurisy

CASE 3—A C had dry rheumatic pericarditis To-and-fro friction sounds were heard over the upper sternal region Pulmonary or pleural involvement was not present Slight dyspnea and a sense of distress were experienced, but aching or pain was not experienced over heart, chest or neck Deep pressure over the precordial region did not elicit tenderness

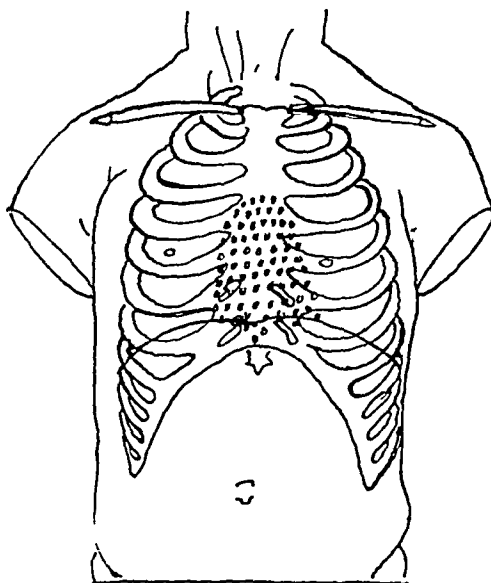


Fig 4 (case 2—2) —Typical dry pericarditis with to-and-fro friction sounds over whole area of the heart Necropsy revealed universal fibrinous exudate over the heart and serous pericardial sac Pain was not experienced in the region of the heart at any time

CASE 4—L McW had dry tuberculous pericarditis There was an old tuberculous lesion of the left apex of the lung, showing in the roentgenogram as a practically healed fibrous thickening The pericardial friction appeared after a chilling and cold in the head Although the friction persisted for several days, there was never any cardiac distress, dyspnea or pain Deep pressure did not cause tenderness over the region of the heart

(C) *Dry Pericarditis Following Coronary Thrombosis*—It is well known that within a few days of the onset of an infectious coronary thrombosis a fibrinous pericarditis is likely to develop Since in these cases there usually is no complication of the pleura or the lung, there is an excellent opportunity to observe any change in the subjective symptoms at the time the pericarditis manifests itself

CASE 1—A E had dry pericarditis appearing on the fourth day after an attack of coronary thrombosis The anginal pain was a dull ache over the heart

with referred pain to the left shoulder. The temperature was elevated. With the development of the friction sounds, the patient was not aware of any new sensation of pain or distress or of aggravation of the angina pains. He died on the seventh day.

CASE 2—C. G. had coronary thrombosis accompanied by anginal cardiac pains in the shoulder and arm, and fever. On the third day after the onset a to-and-fro pericardial friction was heard over the lower sternal region. The cardiac pain was not in any way influenced by the pericarditis and new pain was not experienced. The patient died three weeks later.

CASE 3—E. L. had coronary thrombosis accompanied by typical anginal pain over the heart and slight fever. On the third day after the onset a distinct friction sound was audible over the lower half of the sternum. At the time of the appearance of the pericarditis the anginal pain was no longer severe. The patient was not aware of any new type of pain or of any aggravation of the anginal pain as a result of the pericarditis. After a prolonged period of rest the patient recovered.

CASE 4—H. J. had coronary thrombosis accompanied by continuous cardiac pain and slight fever. On the fourth day, a to-and-fro friction was heard over the apex of the heart. There was no change in the character of the cardiac pain at the onset of pericarditis and no increase in the anginal pain. The patient died on the fifth day.

(D) *Pleuropericarditis, Complicating Dry Pericarditis*—The complication of pleuropericarditis on a true serous pericarditis is responsible for many of the peculiar pain complexes that have caused confusion in diagnosis. A dry pericarditis can be recognized by the presence of a friction rub, synchronous with the heart movements, and usually by that sign only. On the other hand, a pleuropericarditis in the mediastinal regions or along the diaphragm, may not manifest any auscultatory signs, but must be identified by the peculiar and characteristic reference of the pain, which is influenced not by the beat of the heart but by deep inspiration, cough or movements of the chest.

A few illustrative cases are cited.

CASE 1—C. C. H. had pleurisy, pleuropericarditis and pericarditis of unknown infectious origin. On the first day, a pleuropericardial friction rub was heard over the apex region of the heart. A sharp catchy pain was felt at this point and tenderness to pressure. At the same time a sharp pain was felt over the outer third of the trapezius ridge, also tender to pressure. The pain in both locations was induced by deep inspiration and by coughing. These symptoms are explained by a parietal pleurisy and by a pleurisy near the junction of the diaphragm and pericardium. On the second day, a pleural friction was heard above the nipple associated with sharp pain localized over this region. This is undoubtedly due to a restricted parietal pleurisy. On the fourth day a to-and-fro friction was audible over the sternal region, not influenced by breathing and not associated with pain—an involvement of the serous pericardium.

CASE 2—H. P. had pleuropericarditis involving the diaphragmatic pleura, following tonsillitis (fig. 5). A friction rub was heard for two days below the apex of the heart, influenced both by the motion of the heart and by respiration. At the onset the patient complained of a sharp, severe pain in the neck at the junction of the middle and upper third of the trapezius ridge, also of a severe

pain over the navel, with hyperalgesia of the upper left quadrant of the abdominal wall. Both of these points of pain were tender to pressure. After two days, the friction disappeared and the pain gradually subsided.

The roentgen-ray examination showed a definite blurring and cloudiness of the left diaphragmatic pleura especially at the pericardial angle. The referred pain along the phrenic nerve gave a clue to the location of the inflammation, and the referred pain to the abdomen indicated the probable involvement of the margin of the diaphragm with pain referred through the intercostal nerves.

CASE 3—Y had dry pericarditis of rheumatic origin with pleuropericarditis. For several days a to-and-fro friction rub could be heard over the upper and lower sternal region. Pain did not accompany the pericardial friction, when suddenly the patient complained of a sharp pain in the neck in the upper third of the trapezius ridge. This pain was induced by deep inspiration and was probably due to an involvement of the lower part of the fibrous pericardium or to the adjacent diaphragmatic pleura.

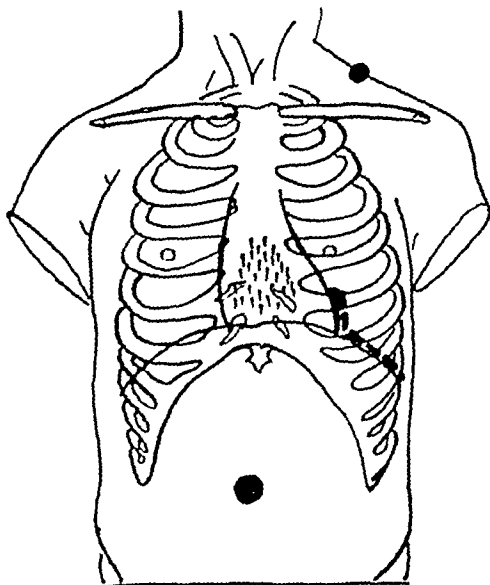


Fig 5 (case 4—2)—Pleuropericarditis, dry serous pericarditis, diaphragmatic pleurisy following tonsillitis. Pain was not felt over the area of the heart. Pain was referred to the neck (from the lower fibrous pericardium and central diaphragmatic pleura), and to the navel (from the outer margin of diaphragmatic pleura) and was induced by deep breath and cough. A roentgenogram showed thickening of the fibrous pericardium and diaphragmatic pleura.

CASE 4—D E had dry pericarditis and pleuropericarditis complicating a rheumatic arthritis. Friction sounds were heard over the lower two thirds of the sternal region at first to-and-fro, later induced only by deep breathing. Endocardial murmurs were not distinguished. Pressure sensation over the sternal region was marked. It felt "as if the chest were bruised inside." A deep breath caused a distinct catch over the sternum like a pleurisy, and it hurt him to move from side to side. Tenderness to deep pressure over the sternum and the parasternal spaces was marked.

The relation of the friction to respiration and the definite relation of the pain to deep inspiration and movement, together with the local tenderness, strongly suggest a mediastinal involvement of the pleura and pleuropericardium.

CASE 5—W M had pericarditis, pleuropericarditis and diaphragmatic pleurisy following osteomyelitis. After a chill and rise in temperature, a friction sound was heard over the lower sternal and parasternal regions, associated with sharp pains in the same location at the end of deep inspiration or cough. This was considered a parietal pleurisy in the anterior mediastinum.

Soon after this two points of acute pain appeared, one over the outer third of the trapezius ridge, the other at the left costal border near the tenth rib, both induced by deep breathing and cough. This was interpreted as a diaphragmatic pleurisy extending over both central and peripheral areas.

On the third day a to-and-fro friction sound was heard over the midsternal region, but not accompanied by pain. This was a serous pericarditis.

SUMMARY

1 Paracentesis of the pericardium at the level of the fifth and sixth interspace lateral to the mammary line elicited pain in the neck at a point

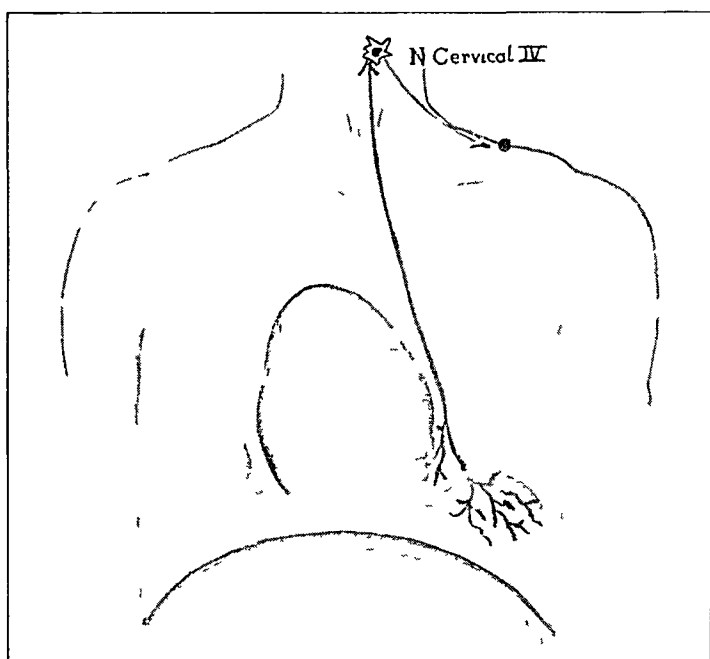


Fig 6—Distribution of sensory fibers of phrenic nerve to the lower part of the fibrous pericardium and the diaphragmatic pleura. The afferent impulses flow into the cervical cord and are reflected to the neck region.

along the trapezius ridge, at the level of the fourth interspace, paracentesis caused no pain. Previous experiments have shown that when the central portion of the diaphragmatic pleura is irritated this also gives rise to pain in the neck. Hence one may infer that the phrenic nerve supplies the central diaphragm and at least the lower portion of the fibrous pericardium with fibers that carry afferent impulses.

2 Exploration of the inner surfaces of the pericardium with a silver wire failed to induce any response of pain in the serous membrane.

3 Pressure on, and scratching of, the pericardial investment of the heart itself did not produce pain, although "tripping" the apex with the wire induced a peculiar feeling of distress and apprehension.

4 In four cases of subacute and chronic pericarditis with large effusion, the patients complained of dyspnea and often of a sense of oppression over the heart, but they did not feel pain over the heart, chest, neck or arm. Deep pressure over the precordium did not cause tenderness.

5 In four cases of simple dry pericarditis with to-and-fro friction sounds, two patients experienced dyspnea and one a "tight feeling" over the heart, the other two did not have distress of any kind. None had sharp pain over the heart, chest or neck. Deep pressure over the precordium did not cause tenderness.

6 In a group of four cases of infective coronary thrombosis, the advent of a dry pericarditis was observed with reference to pain. These patients had had a degree of continuous anginal pain over the cardiac region, but the complication of dry pericarditis did not alter this symptom and did not in any instance give rise to new pain or distress over the heart.

7 From a study of the foregoing groups (paragraphs 5 and 6) one may conclude that a simple dry pericarditis (serous layers) may produce a sense of precordial tightness and moderate dyspnea, but as a rule does not cause subjective symptoms. Actual pain did not occur in any case. These observations taken together with a failure to provoke pain by mechanical irritation of the serous pericardium, lead me to believe that dry pericarditis is usually a painless disease, as Mackenzie has stated.

8 The presence of pain with pericarditis usually indicates the involvement of the tissues outside the pericardium, especially the pleura. Pleuropericarditis may create a variety of pain complexes depending on the location of the disease. Anterior mediastinitis, by involving the parietal pleura, causes direct local pain, aggravated by inspiration, and with tenderness on pressure. A pleuropericarditis near the attachment to the diaphragm, with or without involvement of the diaphragmatic pleura, gives rise to pain in the neck by way of the phrenic nerve. Posterior mediastinitis may involve the parietal pleura and cause dorsal pain. Pleurisy is a common complication of the pericarditis in pneumonia and rheumatism, whereas it is infrequent in the pericarditis of nephritis and other terminal diseases. This probably explains the "painless" character of the nephritic pericarditis and the relatively painful picture commonly attributed to the rheumatic type.

9 There is good authority for believing that pericarditis may at times be associated with angina-like pains, which are explained by Allbutt as being due to the extension of the inflammation in rare cases to the region of the aorta and perhaps even to an invasion of the aorta. Further investigation of the pathologic anatomy in this group is needed.

INTRATRACHEAL INJECTION OF IODIZED OIL

EXPERIMENTAL STUDIES^{*}

B M FRIED, M D

BOSTON

AND

L R WHITAKER, M D

ROCHESTER, N Y

INTRODUCTION

The Combination of Oil with Iodine—The value of iodized oil as a diagnostic agent in diseases of the lungs depends on two properties the opacity to the roentgen ray, owing to the high iodine content, and the nonirritating quality of the substance

Oils combined with iodine or bromine were originally used as therapeutic agents in medicine They were administered by mouth and by subcutaneous injection The conception of using such a combination was associated with the empiric use of cod liver oil, the beneficial effects of which were attributed to the richness of the drug in iodine It was also noted that iodides, valuable medicaments by themselves, were particularly useful when combined with fats Moreover, the tolerance to iodine when combined with lipoids was considered higher than that to other preparations, such as sodium or potassium iodide

It has been shown experimentally that fat which has absorbed about 30 per cent of iodine can be given in large amounts intramuscularly without marked local reaction The older writers produced evidence to show that iodine is partly excreted by the kidneys and partly deposited in the adipose tissue of the organism, where, it was believed, it became identified with the fat of the host In view of this fact, it was considered as a perfect combination for the administration of iodine, particularly when high doses were required

From a chemical standpoint, halogens combine readily with fatty substances or oils when the latter contain unsaturated fatty acids Winternitz¹ was the first to introduce a combination of iodine and oil The iodized oils now used in roentgenology are prepared according to the original method devised by him The content of iodine is, however, increased from 10 and 25 per cent to as high as 40 per cent Only oils

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¹ Winternitz, Hugo Ueber Jodfette und ihr Verhalten im Organism, Ztschr f physiol Chem **24** 425, 1898

of the oleic group, such as poppy oil, are recommended. Oils rich in fatty acids are considered unsuitable for medical purposes.

The Absorbing Power of the Lungs—Physiologists of the first half of the 19th century regarded the lung as an excellent absorbing surface. Colin² injected six liters of water into the lungs of a horse via the trachea without causing any noticeable discomfort to the animal and in another experiment he introduced 25 liters of water within six hours. During the course of this experiment, he withdrew 6 liters of blood without apparent ill effect on the animal. Magendie³ and other physiologists have shown that strychnine and other poisons or toxins are quickly and completely absorbed when injected into the trachea. Thus potassium iodide so introduced appears in the urine within five minutes following the injection.

The brilliant experiments of Claude Bernard⁴ along the same line are in complete accord with those of Magendie and Colin.

The absorbing property of the lungs, and the apparent harmlessness of making injections into them naturally attracted the attention of the clinician. The older physician explained his failure in the treatment of patients with various pulmonary conditions on the basis that these organs could not be attacked directly by drugs. The motto "*Corpora non agunt nisi fixata*" was narrowly interpreted, and methods were looked for to bring the drug in direct contact with the lung. "It sounds illogical," writes Delor⁵ from professor Hayem's clinic, "to think that in angina, cystitis, enteritis, and even in affections of the spinal cord, the very focus of infection is attacked, whereas in pneumonia and bronchitis one treats the patient with drugs absorbed through the stomach and by revulsives."

It may be of interest that the first to apply intratracheal medication was a New York physician, Horace Green⁶. He treated thirty-two tuberculous patients with injections of strong solutions of silver nitrate (6 per cent) intratracheally. His clinical protocols indicated good results, but under the severe criticism of the New York Academy of Medicine he was obliged to discontinue his method. Subsequently it has been used widely in veterinary practice, and it has been revived

2 Colin, J. *Traite de physiologie comparee des animaux*, 1873, vol. 2, p. 108.

3 Magendie, quoted by Colin (footnote 2).

4 Bernard, Claude. *Leçons sur les effets des substances toxiques*, 1857.

5 Delor, J. *Des injections intratracheales vraies et directes dans le traitement broncho-pulmonaires*, These de Paris, 1901.

6 Green, Horace. *De l'emploi des injections dans les bronches et les cavernes tuberculeuses*, *Gazette hebdomadaire de médecine et de chirurgie*, Nov. 30, 1855, p. 831.

as a therapeutic agent in human beings during the last two decades of the 19th century⁷

With the wide clinical application of the roentgen rays, the idea of visualization of the bronchial tree occurred to numerous persons,⁸ but Sicard and Forestier⁹ were the first to make intratracheal injections of iodized oil (lipiodol)¹⁰ This substance is similar to that produced by Winternitz

Recent literature abounds with reports concerning its clinical and roentgenologic use The experiments herein reported are concerned with the action of the iodized oil, introduced intratracheally, on the lungs of animals

EXPERIMENTS AND THEIR INTERPRETATION

Material and Technic—Full grown cats were used in the experiments A carnivorous animal was chosen for the experiments, because it was thought to possess superior ability over herbivorous animals to metabolize quantities of fat

Lipiodol (Lafay) or iodipin (Merck) 40 per cent in amounts varying from 1 to 10 cc heated to body temperature was injected into the trachea of the etherized animals, according to a technic described elsewhere¹¹ Roentgenograms of the chest were taken immediately after injection to observe the distribution of the oil, and also at different intervals to follow grossly the fate of this substance in the chest The animals were killed at intervals of from thirty minutes to four months following the introduction of the oil Removed tissues were fixed and stained in the customary manner and also with Herzheimer stain for the presence of fat

7 Dor, Louis Les injections intratracheales d'huile créosotée chez les tuberculeux, *Rev de méd* **9** 879, 1889-1890 Botey, R Possibilité des injections tracheales chez l'homme comme voie d'introduction des médicaments, *Compt rend Acad d sc* **3** 197, 1890 Clerc, A Injections creosotees intratracheales dans la tuberculose, These de Lyon, 1896 Pillermont, P Action physiologique et chimique des huiles iodees, These de Nancy, 1901 Mendel, H Therapeutique local dans la tuberculose pulmonaire par les injections medicamenteuses intratracheales, *Arch gen de med* **1** 640, 1903 Lafay, L Monographie des huiles iodees et bromees, *ibid*, p 540

8 Guissey and Strodel Injection de l'arbre respiratoire et du parenchyme pulmonaire par la voie transglottique, *Compt rend Soc de biol* **72** 457, 1912 Bossey and Guieysse-Pelissier Recherche sur la penetration d'une substance medicamenteuse dans le poumon sain et tuberculeux par injection tracheale, *ibid* **82** 148, 1919 Lynah, H L, and Stewart, W H Roentgenographic Studies on Bronchiectasies and Lung Abscess After Direct Injection of Bismuth Mixture Through Bronchoscope, *Am J Roentgenol* **8** 49, 1921

9 Sicard, J A, and Forestier, J Methode generale d'exploration radiologique par l'huile iodee (lipiodol), *Bull et mem Soc med d hôp de Paris* **46** 463 (March) 1922

10 Colm, whom I have quoted, relates an experiment by one of his pupils who introduced 500 Gm of oil into the lungs of a horse via the trachea without disturbing the animal

11 Fried, B M, and Proctor, E E The Appearance of Specific Antibodies in the Serum of Rabbits by Intratracheal and Intravenous Injections of Living Tubercle Bacilli, *Proc Soc Exper Biol & Med* **21** 396, 1924

The Reaction of the Animal to the Injected Oil—The cat was not disturbed apparently when the amount of oil injected into the trachea did not exceed 3 or 4 cc. Recovery from the anesthesia was prompt, and the general subsequent behavior of the animal did not differ from that of its normal neighbors. But when the amount of the injected oil was above 4 cc (from 5 to 10 cc), the procedure was followed by loss of appetite and asthenia, with steady loss of weight. This in most cases lasted for about a week and ended in recovery. With 10 cc of iodipin in the lungs, six animals (about 30 per cent) died within from four to five days after the operation, and eight were ill for some time. After death no gross lesions could be found in the lungs or other organs, and it was assumed that iodine poisoning probably caused the rapid demise. A group of six animals that received 10 cc of iodipin survived in our cages for four months in perfect health, and even gained some weight.

From these observations our impression was that the use of moderately small amounts of iodized oil (from about 1 to 1.5 cc per kilogram of body weight) caused no harm to a healthy cat. Doses exceeding that amount appeared to be detrimental to the health of the animal, and not infrequently caused its death.

The Gross Appearance of the Removed Lungs—The cats were killed under deep ether anesthesia. The trachea was usually constricted with a clamp at the height of inspiration so that the organs were moderately expanded, and the lungs were removed and fixed in toto. In a few instances, a 10 per cent solution of formaldehyde was injected into the femoral vein. Fixation by injection of the fixative into the trachea was considered unwise, because this method would disturb or displace the intra-alveolar exudate.

That the oil injected intratracheally reached the alveoli at once was demonstrated by the roentgen ray and also by examining the lungs immediately after injection. In instances in which from 6 to 10 cc of this substance was introduced, the lungs appeared to be markedly distended and uniformly brown, probably due to the iodine (fig. 1). On cut surface these organs were spongy, grossly revealing the presence of oil. In a number of instances, this could be seen as late as from ten to twelve weeks following the injection. With smaller amounts of oil, the brown color of the lungs was distributed in patches. In these areas, the lung was usually more distended than elsewhere. In no instance was pneumonia or other inflammatory processes noted in the experimental animals.

The Persistence of the Oil in the Lungs of Normal Animals—Investigations by older writers (footnotes 1 to 7) who used iodized oil intramuscularly and orally indicate that the introduced drug is first decomposed into its two components, iodine and oil. The iodine is

rapidly eliminated through the kidneys, and the oil undergoes the usual fate of lipid substances introduced into the organism, that is to say, it is decomposed into fatty acids and glycerin and absorbed and oxidized

Recent investigations of intratracheal injections of lipiodol and iodipin seem to confirm the observations made by previous writers, as far as the elimination of iodine is concerned Sicard and his associates,¹² after injecting 5 cc of lipiodol into the lungs of a patient, found iodine in the urine for twenty days, varying in amount from 15 to 200 mg daily Knipping and Ponndorf¹³ found iodine in the urine of patients

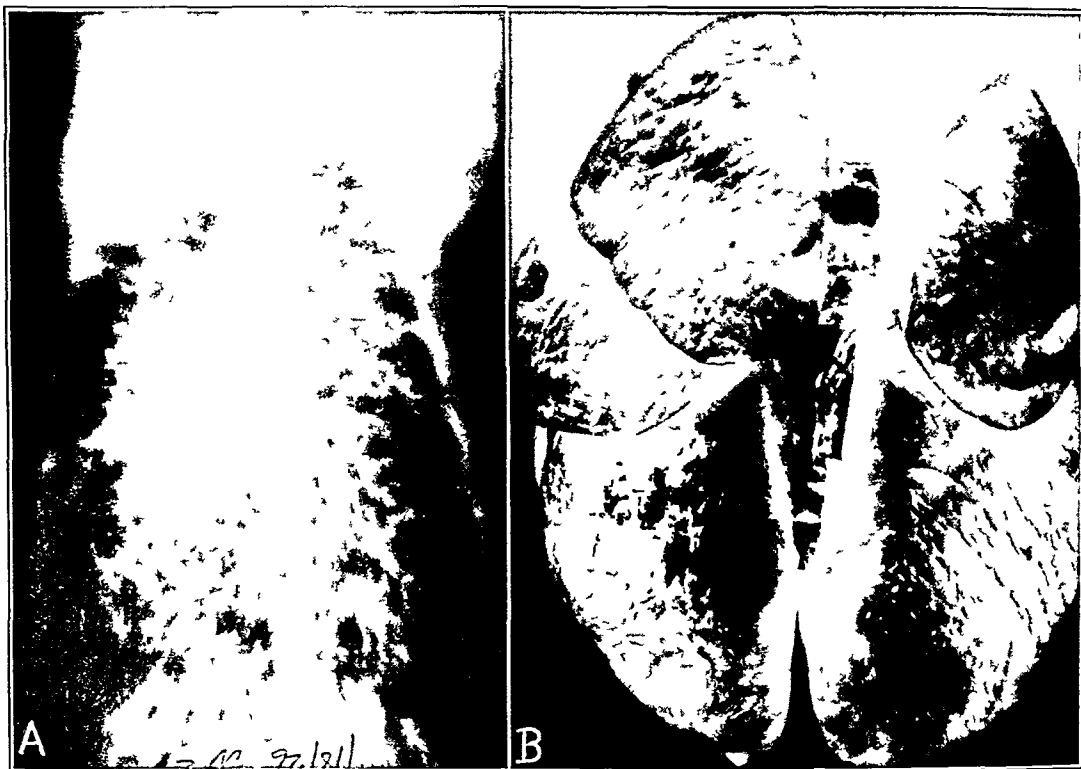


Fig 1—Intratracheal injection of 8 cc of lipiodol *A* is a roentgenogram taken a few minutes after the injection The iodized oil is distributed throughout both lungs, being heavier around the pulmonary root *B*, lungs (two-thirds natural size) from the same cat killed soon after the roentgenogram was taken The lungs are nearly one and a half times larger than usual, but they are spongy and their surface is smooth

a few hours following the intratracheal injection of the oil In one case they found large quantities of iodine in the urine thirty days after the injection of iodipin

12 Sicard, Faber and Forestier Elimination urinaire de l'huile iodée, *Bull et mem Soc med d hôp de Paris* 47 315 (June 23) 1923

13 Knipping H W and Ponndorf, W Ueber die Füllung der Lungen mit Jodol *Beitr z Klin der Tuberkulose* 63 329, 1926

FRIED-WHITAKER—IODIZED OIL

The fate of the oil in the lungs and the reaction which it stirs up there have become questions of importance since the introduction of iodized oil for clinical use

Recent investigations by French physiopathologists indicate that the lungs, besides their function of respiration and elimination of carbon monoxide and water, also play a rôle in the metabolism of carbon substances, particularly lipoids Roger,¹⁴ for instance, compares the pulmonary action on fatty substances to that of the liver on carbohydrates From an anatomic standpoint this is suggestive in the fact

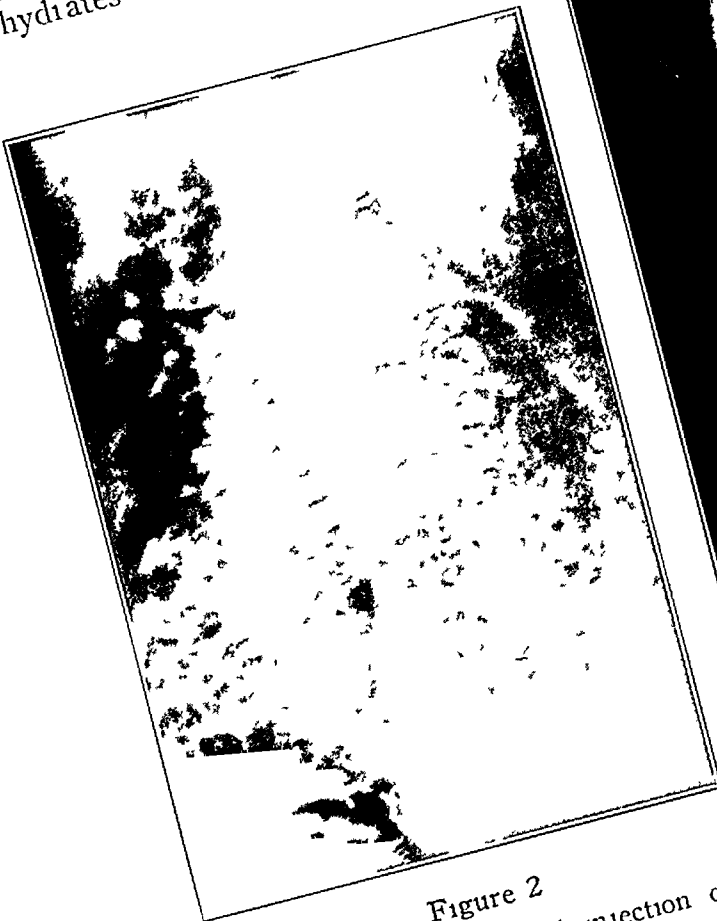


Figure 2

Fig 2—Intratracheal injection of 7 cc of lipiodol Roentgenogram taken about six hours after the injection The oil can be seen at the apex of the left lung The usual arborization distribution of the oil begins to disappear, being replaced by clumps scattered over the lungs

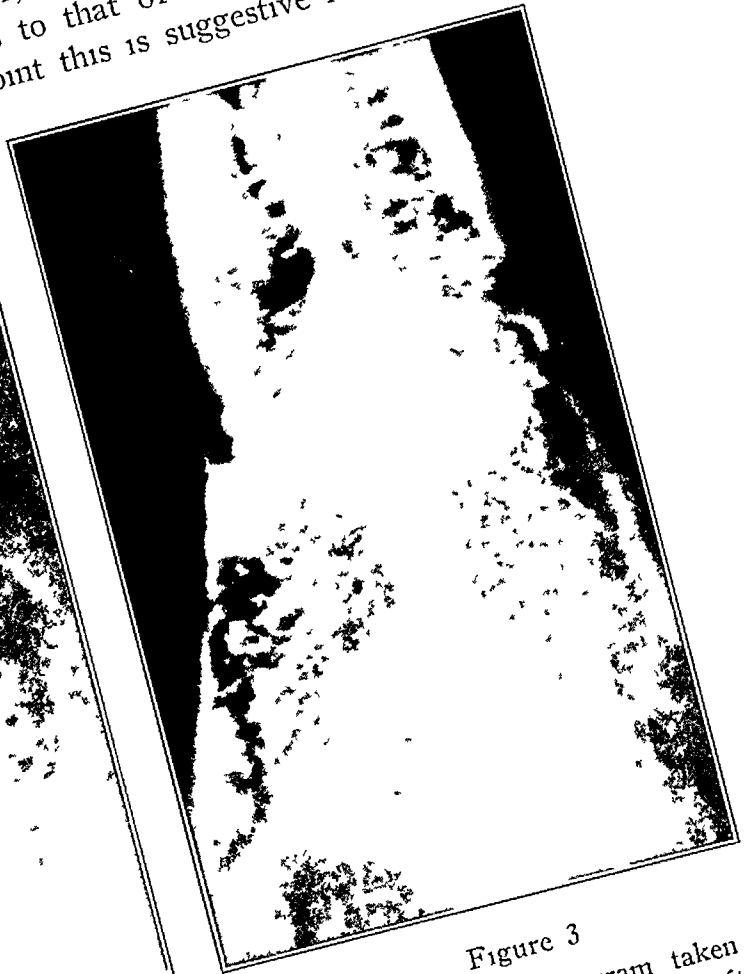


Figure 3

Fig 3—Another cat with 7 cc of lipiodol in the lungs The roentgenogram was taken about fourteen hours after the injection

that absorbed albumins and carbohydrates pass directly into the liver, while fatty substances are transported by way of the lymphatics and the thoracic duct to the right side of the heart and the lungs Roger and

14 Roger, G H, and Bmet, Léon
Rev de méd 42 1, 1925

his associates believe that the action of the pulmonary tissue on lipoids is of double character (1) lipolytic, which consists in the splitting of fat into fatty acids and glycerin, (2) lipodieretic, a term coined by Roger to designate the destruction of fat thus furnishing products which are not further transformed into ethereal extracts. The lipodieresis is attributed by the French workers to a ferment the presence of which is demonstrated by the appearance of a precipitate when phosphate of lime is added to extracts of organs. Histologically, according to Roger and Binet,¹⁴ lipodieresis is effected by the endothelial cells



Figure 4



Figure 5

Fig 4—Roentgenogram of the chest from another animal taken twenty-one days after the injection of 6 cc of iodipin

Fig 5—Roentgenogram taken four weeks after the injection of 6 cc of iodipin

within the capillaries of the pulmonary alveoli. The experiments of Busquet and Vichniac¹⁵ show evidence to the same effect.

Sicard, Faber and Forestier¹² affirm that the lung gets rid of the oil thirty times faster than does muscle tissue or the subarachnoid space.

The results set forth in this paper are based on roentgenologic examination at intervals, of animals with iodized oil in the lungs and

¹⁵ Busquet, and Vichniac, C. Le Poumon organ de fixation elective de l'huile injectee dans le sang, *Compt rend Soc de biol* 84 852, 1921

also on microscopic examination of the lungs made after the animals were killed

As noted, doses exceeding 1.5 cc of iodized oil per kilogram of body weight were poorly tolerated by animals. Some died within a few days following the injection of the oil into the lungs, with signs and symptoms suggestive of iodine poisoning (salivation). Our observations show that even well supported doses (from 1 to 1.5 per kilogram of animal weight) remain within the pulmonary parenchyma for a long time. After a period of four months following the intratracheal injection of lipiodol, traces of the oil could be found in the pulmonary alveoli, particularly around the bronchi and in the vicinity of the hilum of the lungs. In



Fig. 6—Roentgenogram taken about forty days after the injection of 6 cc of lipiodol.

five instances, lungs which appeared clear by roentgenogram about three months after the injection showed the presence of oil on examination with the naked eye as well as with the microscope.

It would seem, therefore, that iodized oil injected intratracheally was not destroyed in the lungs of normal animals with rapidity, but remained there for a considerable time.

The Persistence of Oil in the Lungs of Animals with Respiratory Infection—When iodized oil was injected into the trachea of laboratory animals, a few workers noted disastrous effects—pneumonia, pulmonary abscess and rapid death. Peiper and Close,¹⁶ from experiments on

¹⁶ Peiper, H., and Close, H. Ueber die Grundlagen einer Myelographie, Arch. f. klin. Chir. **134**: 303, 1925.

rabbits, consider the intratracheal injection of iodized oil a dangerous procedure. This may perhaps be attributed to the amount of iodipin injected, possibly to a technical error.

It occurred to us that it would be interesting to compare the rate of disappearance of the oil in animals with a respiratory infection to that in normal animals. Thus iodized oil was injected into the trachea of cats with "snuffles." The lesion during the early stages of this disease is confined to the upper respiratory tract, but the lungs usually show congestion. The animals sneeze a great deal, their respiratory mucosa is hyperemic and secretes mucus abundantly. The experiment that follows is illustrative of a series of six cats.

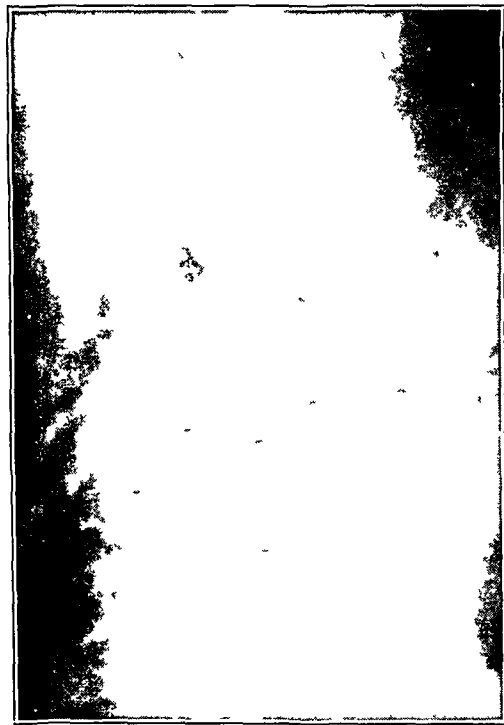


Fig 7—Roentgenogram taken immediately after the injection of 4 cc of iodipin. The injection was performed slowly. The iodized oil coated the trachea and larger bronchi.

Experiment 29 The subject was a cat weighing about 2.5 Kg. It was normal except for "snuffles" at an early stage.

On Nov 7, 1926, 4 cc of warm iodipin (Merck) was injected into the trachea. A roentgen-ray examination of the chest a few minutes after the injection showed that the oil was distributed in the lungs in the usual arborization fashion with filling of the alveoli. During the five to six days following the injection, no changes of any kind could be noted in the animal. The infection ran its usual course, neither the nasal mucous secretion nor the sneezing apparently being influenced by the injection of iodized oil.

Roentgen-ray examination of the chest every fifth day showed that the oil "melted" away rather rapidly. At first, the periphery of the lung became clear,

this was followed by an accumulation of "clumps" of the substance in the lower and middle parts of the pulmonary parenchyma. On the twentieth day, oil was still visible at the roots of both lungs. At the end of the sixth week, a roentgenologic examination of the chest showed that the lungs were clear. With the microscope only small droplets of oil could be found at the pulmonary hilum within the pulmonary alveoli, around the larger bronchi and also between the mucous glands. The roentgen-ray as well as the microscopic examination showed the persistence of rather considerable amounts of the oil throughout the lungs in control animals.

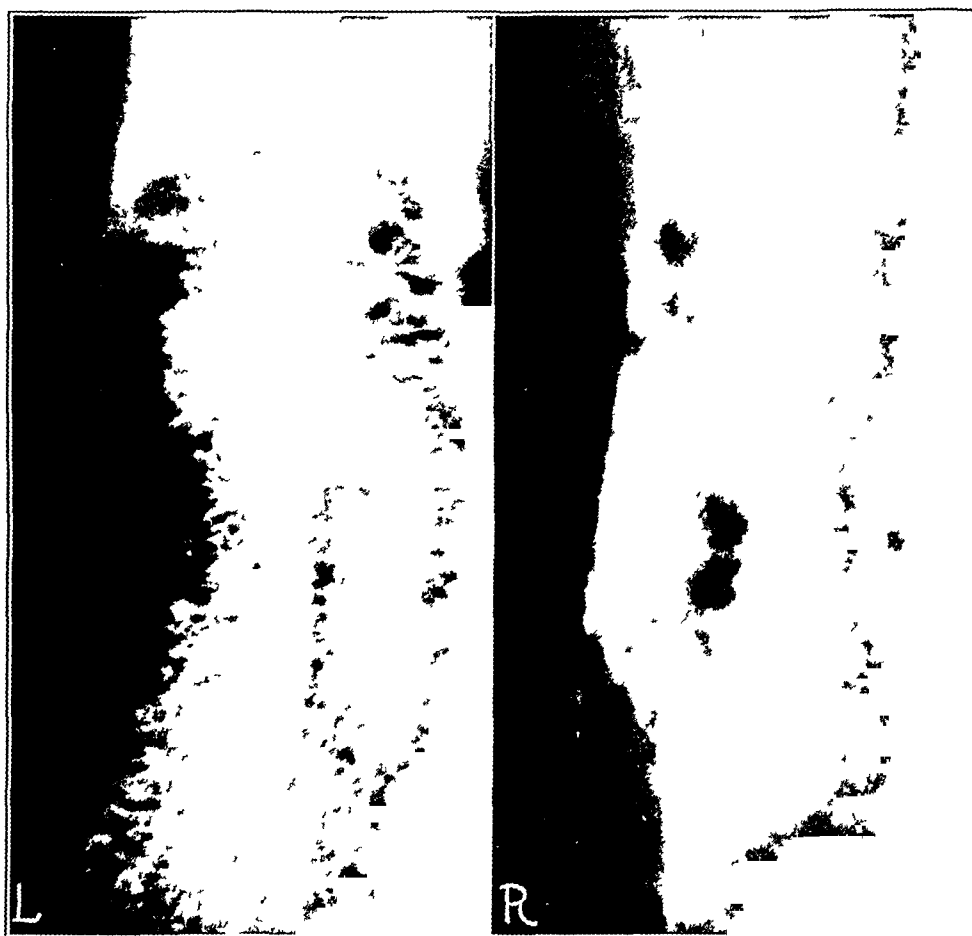


Fig 8—*L* is a roentgenogram taken immediately after the injection of 8 cc of iodized oil into a cat, and shows the powdery distribution of the substance, *R* was taken ten days after the injection. Instead of the fine mottling seen in *L*, the oil here is rather dense, being particularly heavy along the spine.

The oil in these six cases apparently did not influence the disease. Furthermore, these cats freed themselves from this substance much quicker than their healthy fellows, this was probably due to frequent sneezing which "drove" the oil from the pulmonary alveoli into the bronchi, whence it reached the pharynx and was swallowed. Coughing may therefore be an important factor in the elimination of the oil from the chest of persons with pulmonary disease.

The action of the hypothetic pulmonary enzyme of Roger on the introduced fat is apparently slow. If iodized oil injected into the chest may produce damage before it is finally excreted, it would be advisable to induce coughing in noncoughing patients or to institute some kind of a posture drainage by which the oil would be quickly eliminated.

The Histologic Reaction of the Lungs to Iodized Oil—The animals, as already noted, were killed at intervals of from thirty minutes to four months following the intratracheal injection of the oil. The pulmonary reaction to the introduced substance was as follows:

The fat seen in the alveoli as round globules of different size was attacked almost instantaneously by cells which were easily identified as

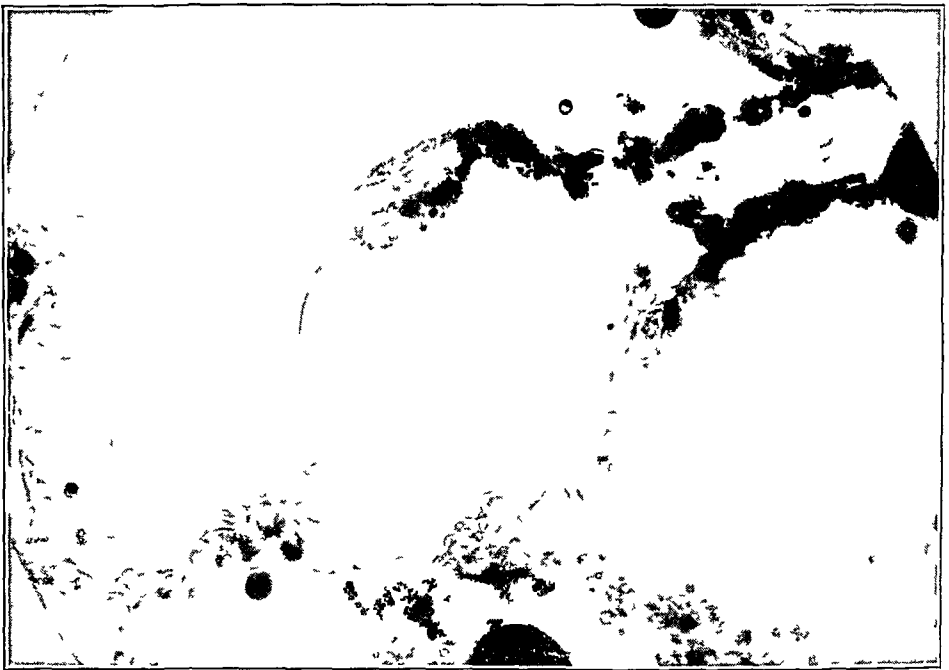


Fig 9—Intratracheal injection of lipiodol. A frozen section stained with Herxheimer's stain for fat from the lung of a cat killed about forty-five minutes after the injection. The alveoli are distended, the alveolar wall is "naked." In one place the cells "lining" the air sac are gathered in a small group showing fatty granules in their cytoplasm, reduced from a magnification of $\times 850$.

large mononuclear phagocytes—macrophages (figs 9 and 10). These cells with familiar morphology showing numerous vacuoles in their cytoplasm were found within the alveoli surrounding the lipid material as if trying to devour it or to wall it off. Thirty minutes after the injection a number of them showed numerous fatty granules in their cytoplasm, as was demonstrated by the scharlach R stain. The walls of the alveoli showed slight swelling and also the presence of fatty granules. The cellular elements here seemed to be increased in number, some of the cells being readily identified as macrophages by their morphology and by the way they had engulfed the oil.

The reaction of the cells "lining" the air sacs is of interest. These cells, which usually appear as small irregularly round or polygonal cells or as flat endothelioid cells resembling the Kupffer cells, showed an increase in size and took on an epithelial-like aspect. Normally, they are more or less separated from each other by wide spaces, and in areas their presence cannot be demonstrated, thus giving the impression that the alveolar wall is "uncovered" (fig 9). But here, due to their "swelling" and proliferation, they appeared to line the alveolar wall in a syncy-

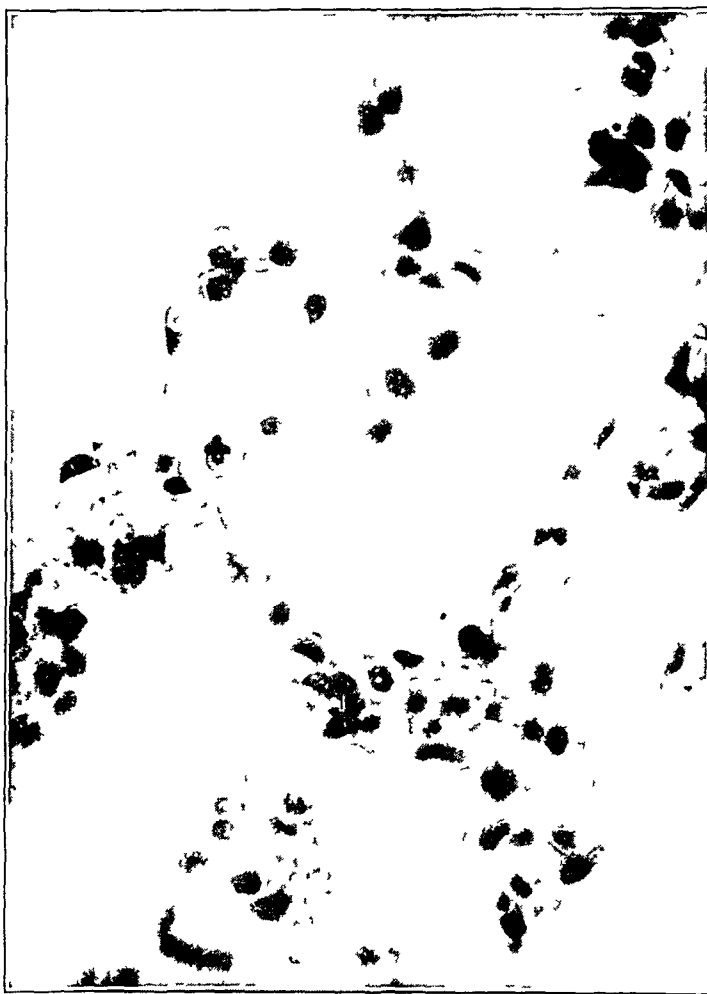


Fig 10—A section stained with hematoxylin and eosin from the lung of a cat killed thirty minutes after the injection of iodized oil. The large cells with a deeply stained nucleus having a wide rim of foamy cytoplasm are macrophages. Some of the macrophages lie free in the air sac, others "line" the wall of the alveolus, and still others are seen within the contour of the dilated capillary. These cells only respond to the oil injected into the lungs by way of the trachea, reduced from a magnification of $\times 850$.

tium-like manner. In some areas they were seen singly and in others in rows along the wall of the air sac. They contained oil droplets gathered in groups like the granules of neutral red in the "supravitaly stained clasmotocytes" of some writers.

Cells at different stages of transformation from the flat, endothelioid to the plump epithelial-like cells were seen within thirty minutes following the injection of the oil. During the subsequent days, the reaction increased in quantity but remained qualitatively the same. The cells "lining" the alveoli with or without fatty droplets in their cytoplasm detached themselves from the wall of the air sac singly and en masse to form the intra-alveolar exudate.

The "desquamated" cells and those which had migrated from the loose connective tissue of the alveolar septums gathered in certain areas and formed tumor-like masses. Here the alveoli collapsed and the normal architecture of the lungs was destroyed. The reaction apparently reached its climax within the first few days following the introduction of the oil. It seemed to remain stationary for about one month, at which time it began to disappear. The process was, however, slow, three months after the introduction of the iodized oil, the "macrophage exudate" could be seen here and there, and droplets of oil could be detected.

The capillaries of the lungs showed marked congestion for from one to two weeks after the operation when large doses of oil had been injected. But with from 2 to 4 cc. of oil in the pulmonary parenchyma the congestion was ephemeral, lasting one or two days only. The endothelium of the capillaries showed possibly slight swelling, but no proliferation. In a few instances, a drop of oil could be found in the cytoplasm of these cells. At times, droplets of oil could be seen inside the lumen of a capillary.

The bronchi showed slight increase in secretion but no proliferation or desquamation. There was some increase in the lymphoid tissue, particularly around the vessels and the bronchi.

Interpretation of the Histologic Picture—The oil stirs up a reaction confined to the cells lining the pulmonary alveoli, which are commonly designated as respiratory epithelial cells. These cells, when activated by the introduced oil, begin to swell, taking on an epithelial aspect. They phagocytose the oil with avidity, storing it in their cytoplasm as coarse and fine granules.

This part of the problem is therefore of interest in that it involves the question of the origin of the macrophages in the lungs and also of the nature of the cells lining the wall of the pulmonary alveoli. This subject has been treated by one of us at some length in a previous investigation on the effect of intratracheal injections of vital dyes.¹⁷

17 Fried, B. M. The Origin of Histiocytes (Macrophages) in the Lungs. An Experimental Study by the Use of Intratracheal Injections of Vital Stain, *Arch. Path.* 3: 751 (May) 1927.

Suffice it to say that the present study with iodized oil is in complete agreement with the conclusions previously drawn from the investigation with the vital dyes. It may be stated (1) that the phagocytes found in the pulmonary alveoli are histiocytes or macrophages, (2) that the bulk of the macrophages originate from the cells lining the alveolar wall, and (3) that these cells are to all appearances not epithelial but of mesenchymal origin and ought to be regarded as cells of the reticulo-endothelial apparatus (macrophage apparatus). If, then, one is to suppose that the lungs are provided with a ferment splitting or destroying fat (lipolysis and lipodieresis) as stated by Roger and his associates, it ought to be sought, not in the capillary endothelium (Roger and Binet) but in the local macrophage apparatus.

SUMMARY AND CONCLUSIONS

Iodized oil injected into the lungs of cats by way of the trachea is well tolerated when the amount does not exceed 1.5 cc per kilogram of the animal's weight.

The oil remains in the lungs for long periods, in a number of cases, animals killed four months after injection showed the presence of this substance in the air sacs.

In a few instances, iodized oil was injected into the lungs of cats with a respiratory infection (snuffles). These animals got rid of the oil much quicker than the healthy cats. This may be explained on the supposition that the animals with "snuffles" squeezed the oil from the lungs into the pharynx by sneezing, from whence it was swallowed.

The pulmonary reaction stirred up by the oil in the lungs is confined to the cells "lining" the alveolar wall, commonly spoken of as the respiratory epithelial cells. These cells, being normally macrophages in a resting state, transform themselves under the influence of the introduced oil into wandering phagocytes devouring the oil and storing it in their cytoplasm as fine and coarse granules. These cells likewise proliferate, forming large cellular masses resulting in localized destruction of the normal pulmonary structure.

In none of the forty-four cats used did the iodized oil lead to sclerotic changes in the lungs.

Book Reviews

DIE KAROTISSINUSREFLEXE AUF HERZ UND GEFASSE, VOM NORMAL-PHYSIOLOGISCHEN, PATHOLOGISCH-PHYSIOLOGISCHEN UND KLINISCHEN STANDPUNKT
By DR H E HERING, Professor der Normalen und Pathologischen Physiologie an der Universität in Köln A RH Price, paper, 9 marks, bound, 10 50 marks Pp 150, with 45 illustrations Dresden and Leipzig Verlag von Theodor Steinkopff, 1927

This monograph is a summary of the studies published in various medical journals and scientific archives during the last few years by the author and his co-workers on the mechanism of the slowing of the heart on the pressure of the carotid arteries in the neck Previous to the work done by Dr Hering it had been generally assumed that the slowing of the heart after pressure on the carotid artery was due to direct pressure on the cardio-inhibitory fibers of the vagus nerve Dr Hering seems to have shown that the vagus trunks in the neck are resistant to mechanical stimulation, and that the phenomenon mentioned is due to a specific reflex The focus for the sensory nerve distribution of the reflex is in what Dr Hering calls the "carotid sinus," that is, the enlargement of the carotid at the point of division of the internal and external carotid arteries This region of the artery is supplied by the sensory fibers from the glossopharyngeal nerve, and the stimulation of these sensory fibers causes reflex inhibition of the heart, as well as lowering of the blood pressure Dr Hering has shown that this mechanism is in tonic activity, that is, if the ninth nerve is sectioned, or if this so-called "carotid sinus" is completely denervated, the heart becomes permanently accelerated It would, therefore, seem that this new mechanism is a part of the well known depressor system, the sensory end of the reflex being distributed mainly in the ventricles and in the aorta

Dr Hering extended his experimental studies into the clinical field, and presents some evidence that in hypertension and in sclerosis of the arteries the reflexes from the carotid sinus to the heart and vasomotor center are modified

Students and practitioners interested in the physiology and pathology of the vascular system may peruse the monograph with profit

A TEXT-BOOK OF MEDICINE By 130 American Authors Edited by Russell L Cecil, M D, Assistant Professor of Clinical Medicine, Cornell University, Medical School, New York Price, \$9 Cloth Pp 1,500, with illustrations Philadelphia W B Saunders Company, 1927

This book should prove especially acceptable to students of medicine, since most of the contributors are teachers in university medical schools The book is easily the equal of any, and it is superior in many respects to most of the textbooks of a single volume prepared by one author This is true in part, because, as the editors state, the rapid growth of medical science during the last few years has made it almost impossible for one person to master the entire field It is safe to predict the wide use of this text in medical colleges Physicians will find it an authoritative and up-to-date work, presenting in concise manner material that would otherwise be available only in bulky systems of medicine

Each disease or group of diseases is discussed by a writer particularly interested in that subject There are 130 American contributors, each of whom is a student or investigator of the subject on which he has written The general sense of proportion as regards relative space for the presentation of the various diseases is preserved From a conservative standpoint practically all conditions worthy of mention are included In a treatise of this scope minor omissions are unavoidable, for example, massive collapse of the lungs has not been described The final section on disorders of the mind is a timely addition

Particularly to be commended is the inclusion, after most of the articles, of important references concerning the various subjects

This well planned and well written textbook is strongly recommended to students and practitioners

MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD'S WAR,
Volume 6 Sanitation in the United States, by COL W P CHAMBERLAIN,
MC Sanitation in the American Expeditionary Forces, by LIEUT COL
FRANK W WEED, MC Price, \$3.25 Washington, D C Government
Printing Office, 1927

This volume contains a great deal of information of interest to the practicing physician, to those interested in sanitation and to epidemiologists. The entire problem of sanitation as carried out in the World War is given in detail. This includes selection of camp sites, housing, food, disposal of garbage and sewage, water supply, control of flies, mosquitoes and vermin, hospital isolations, physical examinations for detection of disease in its incipency, and other problems.

A chapter is devoted to the influenza epidemic of 1918, showing the rapidity with which disease spreads and the futility of attempts to control it.

The rations of various organizations and changes from time to time are discussed in detail. The rations of the United States army are compared with those of the English, German and French armies.

It is impossible to give in a brief review an insight into the great work done by the Department of Sanitation. It is a valuable record of what was done by this department during the World War.

THE PSYCHOLOGY OF MENTAL DISORDERS By ABRAHAM MYERSON, M D
Price, \$1.40 Pp 135 New York The Macmillan Company, 1927

This book is written primarily for intelligent, nonmedical readers and aims to give the main facts about mental disease. The author says that the publicity given to physical diseases has, in large part, done away with many of the misconceptions regarding such matters as diet, infectious diseases, tuberculosis, cancer and the like, and adds "Partly because psychiatry as a branch of medicine has not achieved the scientific status of the other specialties, partly because the treatment of mental diseases is far from satisfactory, the program called mental hygiene has lagged behind in results and in organization, though much valiant work is being done in this direction. It is the province of this book to dispel, insofar as I am capable of doing so, some of the popular ignorance on this subject." He points out that the term insanity is legal and arbitrary, and divides the mental diseases in two main groups, the major mental diseases, or psychoses, and the minor ones, the psychoneuroses, such as hysteria and neurasthenia. The discussion of the psychoneuroses, particularly, is highly recommended as lucid, fascinating and most sane and sensible. Even physicians who consider themselves thoroughly familiar with the subject will profit by reading Myerson's chapters. Mental deficiency, crime and heredity are also discussed in a masterly manner. In short, the book is valuable, and because of its conciseness and brevity, it can be read in a few hours.

CITY HEALTH ADMINISTRATION By CARL E McCOMBS, M D Price, \$5.50
Pp 511 New York The Macmillan Company, 1927

This book is divided into three parts: (1) municipal health functions, (2) organization and administration of preventive functions of sickness, and (3) organization and administration of treatment functions of sickness. In the language of the author, it is designed to be most useful to the person without professional training or experience, whether he is a teacher or student of government, a public official or a man in the street who wants to know what health benefits he should receive for his tax payment.

Dr McCombs presents an analysis of city health administration which should adequately meet the needs it aims to supply. It does not make any

pretense to technical authority, but presents the essentials in the health field, at all times stressing an educational feature

This book should be read by students of public health, particularly public health administrators, as it contains comparative data which are of value

Too much emphasis, however, is placed on one large department of one large city. A comparison of the standards, of a group of cities would have been better

A selected bibliography is presented which, apparently, is fairly representative of the particular subjects treated

DISEASES OF THE SKIN By JAMES H SEQUEIRA Ed 4 Price, \$10 Pp 644, 56 plates in color, and 309 text figures New York The Macmillan Company 1927

It is unfortunate that in the revision of this generally excellent work, a systematic treatise on diseases of the mucous membranes was not included. That would have made it much more helpful to the student and general practitioner for whom it is intended. Other changes are needed such as more adequate description of many important lesions, as syphilitic condylomas. Leukoplakia, for instance, is casually mentioned and pictured with syphilis, leading to the incorrect inference that it is a lesion of that disease. The great importance of the search for *Spirochaeta pallida* in the diagnosis of primary syphilis is not sufficiently stressed.

On the other hand, the book is well written, largely from the author's own experience, and the illustrations, for the most part original, are excellent. The work of the printer has brought them out to the best advantage. The bibliography is select, and it is gratifying to find that American work has not been overlooked. The addition of much new material, largely on tropical diseases brings the work much more nearly down to the minute than is usual with textbooks. The author is to be congratulated on the increasing success of his etiologic classification.

LECTURES ON INTERNAL MEDICINE By KNUD FABER, M D, Professor of Internal Medicine University of Copenhagen, Denmark Cloth Price, \$3 Pp 147, with illustrations New York Paul B Hoeber, Inc., 1927

During 1926, while on a tour through the United States, Professor Faber lectured before many medical societies and schools. The four chief lectures are presented in book form and are well illustrated. The addresses given here were as follows: "The Etiology and Pathogenesis of Achylia Gastrica," the Hatfield Lecture delivered at the College of Physicians in Philadelphia, "The Intestinal Origin of Pernicious Anemia," presented before the American College of Physicians at Detroit, "Benign Glycosuria," the Herter Lecture at Johns Hopkins University and "Historical Outline of Medical Therapy," Harvey Lecture, given before the New York Academy of Medicine.

PRACTICAL LECTURES ON THE SPECIALTIES OF MEDICINE AND SURGERY Delivered Under the Auspices of the Medical Society of the County of Kings, Brooklyn, New York Second series, 1924-1926 Cloth Price, \$7 Pp 590, with 110 illustrations New York Paul B Hoeber, 1927

As indicated in the title, this work is an extension of the first series of practical lectures which were published in 1925. They cover a wide range of subjects of interest to all medical men. Each lecture is complete in itself, and represents the present day knowledge and opinion of each subject discussed. They were delivered chiefly by physicians and teachers of prominence in the New England states. Numerous illustrations enhance the value of the work. There is every reason to predict that this series of lectures will be received with as great enthusiasm and commendation as was the first series.

EXPERIMENTS ON WATER AND SALT DIURESIS *

DAVID M RIOCH, M D

ROCHESTER, N Y

That a typical diuresis follows the ingestion of large amounts of water has been known for some time, but the mechanism by which the water is conveyed from the intestine to the kidneys and the factors stimulating the kidneys to action, whether they are hormone, vascular, nervous, or physicochemical, are not yet proved beyond question Engel and Scharl,¹ using the refractive index of the serum, Macallum and Benson,² using the red blood cell count, Haldane and Priestley,³ and Adolf,⁴ using hemoglobin determinations, found that no dilution of the blood is measurable by these methods when large amounts of water are drunk, although a marked diuresis is produced Priestley⁵ did not find any dilution of the hemoglobin, but a decrease of from 2 to 5 per cent in the conductivity of the serum, indicating a proportionate dilution of the plasma electrolytes He also found that when an almost isotonic salt solution is drunk the hemoglobin is diluted, the conductivity rises and the diuresis is slight in comparison to that produced by water In 1921,⁶ Priestley carefully determined the water content of the whole blood before and after water was drunk His method consisted in weighing the samples, drying them over phosphorus pentoxide and reweighing He found from 2 to 3 per cent more water in the samples taken after 2,000 cc of water was drunk, but chloride determinations done at the same time showed a 5 or 6 per cent dilution of the total chlorides He also found that 15 Gm of sodium chloride produced a diuresis of from 70 to 90 cc an hour for several hours Adolf⁴ found

* From the laboratories of the Department of Medicine, Johns Hopkins University Medical Department, Baltimore

1 Engel, Karl, and Scharl, P J Die Konzentrations veränderung des Blutserums nach Wasseraufnahme, *Ztschr f klin Med* **60** 225, 1905

2 Macallum, A B, and Benson, C C On the Composition of Dilute Renal Excretions, *J Biol Chem* **6** 87, 1909

3 Haldane, J S, and Priestley, J G The Regulation of Excretion of Water by the Kidneys, *J Physiol* **50** 296, 1916

4 Adolf, E F The Regulation of the Water Content of the Human Organism, *J Physiol* **55** 114, 1921, Chemical Regulation of the Activities of the Human Kidney, *Am J Physiol* **63** 432, 1923

5 Priestley, J G The Regulation of Excretion of Water by the Kidneys, *J Physiol* **50** 304, 1916

6 Priestley, J G The Regulation of Excretion of Water by the Kidneys, *J Physiol* **55** 305, 1921

that water taken in excess of that required by the body is promptly excreted, that an isotonic salt solution (sodium chloride) produces a diuresis much less in rate, but lasting much longer than that produced by water, that a hypotonic solution acts as a mixture of isotonic solution and water, the excess water being rapidly excreted, and that a hypertonic solution produces a prolonged diuresis at a rate of from 100 to 200 cc an hour

In regard to the stimulus of water and salt diuresis, it appears that the osmotic pressure of the blood⁶ is responsible, but as comparatively few experiments have been done and few points determined it was thought well to repeat the work, using more subjects, and taking more frequent blood samples, so as to determine the form of the curve of the dilution of the electrolytes

METHODS

The subjects for these experiments were healthy white adults, from 20 to 30 years of age, teachers and medical students at the Johns Hopkins Hospital

In every case, the subject took no food from supper the evening before the experiment was begun until after it was ended. Water was drunk as desired until the beginning of the experiment, after which water was not taken except as noted in the protocols. During the experiments, the subjects worked in the laboratory or on the ward

Blood was drawn without exposure to air from a vein of the arm either in well fitting Record syringes or in oiled syringes and was immediately injected through capillary glass tubes under oil in heavy walled Pyrex test tubes with a capacity of 10 cc. A one-hole rubber stopper was then inserted and the tube centrifugalized. The serum was removed with pipets with capillary tips. The samples for the refractive index and the determinations of viscosity were drawn in dry syringes and were not put under oil. The blood was drawn under stasis,⁷ except in experiments 8 and 9, the stasis, however, was not

⁷ It has been shown by Dautrebande, Davies and Meakins (*The Influence of Circulatory Changes on the Gaseous Exchanges of the Blood*, *Heart* **10** 133, 1923), and more recently by Peters, Bulger, Eiseman and Lee (*Total Acid-Base Equilibrium of Plasma in Health and Disease* IV *The Effects of Stasis, Exercise, Hyperpnea, and Anoxemia, and the Causes of Tetany*, *J Biol Chem* **67** 175, 1926) that prolonged venous stasis causes concentration of the peripheral blood, amounting in some cases to 30 per cent. In the experiments of Dautrebande, Davies and Meakins, however, stasis was maintained for twenty-five minutes and more, and "until the forearm and hand had developed a marbled cyanotic appearance and were quite painful" (Peters et al). In the experiments reported here, the stasis was not maintained in any case for more than two minutes, usually considerably less and in two experiments in which no stasis was used the results were the same as in similar experiments in which stasis had been used. It is therefore felt that the amount of stasis present in these experiments did not appreciably affect the results

maintained for more than two minutes. No attempt was made to maintain the original carbon dioxide tension of the serum after centrifugalizing, as in preliminary experiments, it was shown that resaturating the serum with alveolar air did not significantly change its conductivity. This has also been shown by Atchley, Loeb, Benedict and Palmer.⁸ In preliminary experiments, it was also shown that the conductivity of pig's serum, before and after being put through the same procedure that the blood underwent, did not change by more than 0.04 per cent.

The conductivity was determined by the Wheatstone bridge method, a Kohlrausch bridge and Cuthiss coils designed by Leeds and Northrup, and a 500 cycle alternating current from a constant speed generator being used. The apparatus was calibrated against standard resistances from the Department of Physiology. The cell was in the form of a flattened Ostwald pipet containing approximately 1.8 cc. The electrodes, 1 sq. cm. in area and about 0.5 cm. apart, were fixed in the sides of the pipet, from which glass tubes containing mercury made connections with copper wires from the bridge terminals. The lower end of the cell was closed with a clean, one-holed rubber stopper and a glass rod. Constant readings were obtained after washing the cell three times with 0.5 cc. quantities of serum, so that a complete determination could be readily made on 4 cc. of serum. The cell was made to order by Machtlet and Co. of New York and was satisfactory. The cell constant was determined before and after each series of determinations with a fiftieth normal solution of recrystallized potassium chloride in conductivity water. It was found to be approximately 0.327. Three resistances were used in each determination and the results averaged. All determinations were made in a water bath having a constant temperature within a fraction of a degree of 25 C. and corrected to 25 C., a 0.2 per cent increase in conductivity per 0.1 C. rise in temperature being assumed.

The effect of the proteins on the conductivity has not been considered in the calculations, as the determinations of protein were not sufficiently reliable to warrant their use for this purpose, as described below. However, when the effect is appreciable, it will be pointed out in the discussion.

The dilution of the proteins was measured either by the change in the refractive index and viscosity of the serum or by determining the total nitrogen. The refractive index of the serum was determined with an Abbe refractometer, the refractive index of distilled water

⁸ Atchley, D. W., Loeb, R. F., Benedict, Ethel M., and Palmer, W. W. Physical and Chemical Studies of Human Blood Serum. *Arch. Int. Med.* **31**:606 (April) 1923.

being taken before each determination. The results are recorded as the refractive index of the solids, being the difference of the refractive indexes of the serum and of distilled water. The viscosity was determined with a Hess viscosimeter. The total nitrogen was determined by

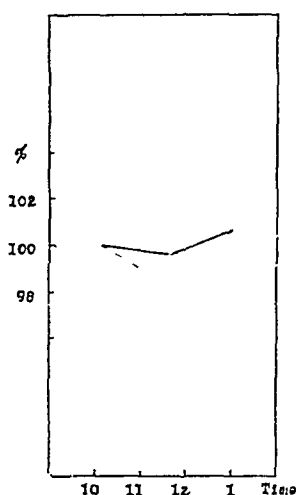


Chart 1

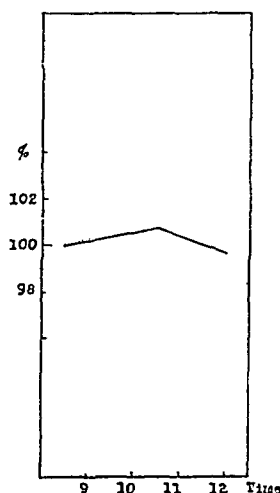


Chart 2

Chart 1 (experiment 1) —Control experiment. In this and in the following charts, the solid line indicates the conductivity of the serum calculated as percentage of first or control sample, the dotted line, refractive index of serum solids or protein by Kjeldahl digestion calculated as percentage of initial sample.

Chart 2 (experiment 2) —Control experiment

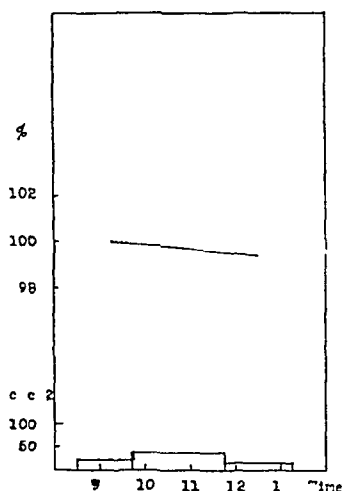


Chart 3 (experiment 3) —Control experiment. In this and in the following charts, the crooked line indicates the rate of secretion of urine in cubic centimeters per hour.

Kjeldahl digestion, 1 cc of the serum on which the conductivity had been determined being used. The same pipet was used in each case, and duplicate determinations were run in the majority of cases. The results are recorded as percentage of protein, the nonprotein nitrogen being disregarded, as the changes it might undergo would not produce

a significant error. Unfortunately, the determination of the proteins was not accurate enough to be of much value, due to the small amount of serum available. They are given, however, as it is felt that they indicate at least roughly the trend of dilution, and are significant in the experiments with Locke's solution and concentrated salt solution. The probable error amounts to about 5 per cent.

Protocol of Experiment 1

March 30, 1923		No water									
		Blood					Urine				
Time	Notes	Specific	Per	Refrac-	Per	Vis-	Amt	Rate	Specific	Specific	
		Con- ductivity	Cent	tive Index	Cent	cosity			Gravity	Con- ductivity	
10 10	Blood	0 01195	100	0 0177	100	—	} Urine not collected				
11 40	Blood	0 01190	99 6	0 0174	98 3	—					
1 00	Blood	0 01203	100 6	0 0174	98 3	—					

Protocol of Experiment 2

March 31, 1923		No water								
		Blood					Urine			
Time	Notes	Specific	Per	Refrac-	Per	Vis-	Amt	Rate	Specific	Specific
		Con- ductivity		tive Index						
8 30	Blood	0 01204	100	0 0175	100	1 725	}	Urine not collected		
10 30	Blood	0 01213	100 7	0 0177	101 1	1 775				
12 00	Blood	0 01199	99 6	0 0177	101 1	1 750				

Protocol of Experiment 3

June 31, 1923		Blood					Urine			
Time	Notes	Specific	Per	Refrac-	Per	Vis-	Amt	Rate	Specific	Specific
		Con-	Cent	tive	Cent	cosity			Gravity	Con-
8 30	Bladder emptied									
9 00	Weight, 68,350 Gm									
9 15	Blood	0 012233	100	0 0169	100	1 85	27	21 5	1 034	
9 45	Urine									
10 30	Blood	0 012204	99 8	0 0169	100	1 84	37	37	1 033	
11 45	Urine									
12 30	Blood	0 012146	99 4	0 0172	101 8	1 87	23	15 5	1 032	
1 15	Urine									
1 30	Weight, 67,650 Gm									

Urine was collected as noted in the protocols, and the volume measured with an accuracy of 2 per cent. Either the specific gravity or the conductivity or both was determined, an ordinary hygrometer and the conductivity apparatus described above being used.

EXPERIMENTS

Experiments 1, 2 and 3 (figs 1, 2 and 3) were run as controls, no water being taken. The irregular variation of the conductivity, amounting to 11 per cent in experiment 2, is possibly due to the frequent changes in blood flow and metabolism that are bound to occur in the arm of an individual who is moving about at work.

Six experiments (figs 4, 5, 6, 7, 8 and 9) were done in which water was taken. The curve of the diuresis is similar in all, an abrupt rise to a peak in from one to two hours, and a more gradual decline. In experiment 6, the decrease in conductivity parallels the rate of diuresis, but in the other experiments (except experiment 7), there is a tendency for the diuresis to lag from one-half to one hour behind the drop in conductivity. The greatest change in conductivity noted is 3.8 per cent in experiment 5.

As stated, the protein curves are too irregular to warrant any conclusions, except that in only one case, experiment 7, is there any definite dilution.

In experiment 7, a small volume of distilled water was taken, producing a definite diuresis which is contrary to what Hashimoto⁹

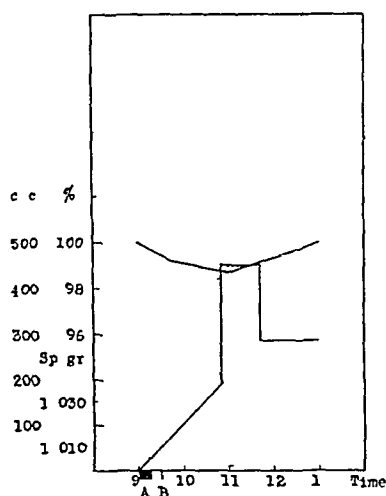


Chart 4

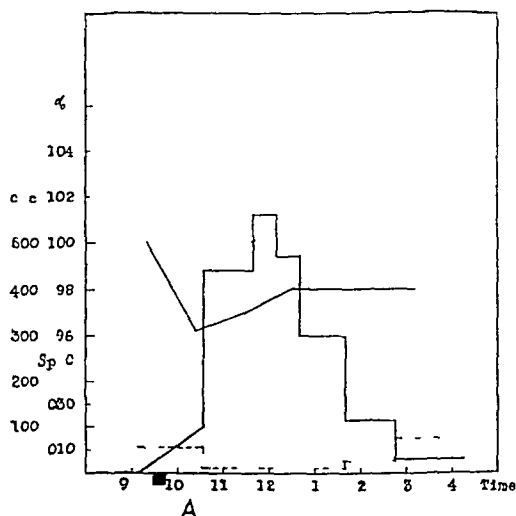


Chart 5

Chart 4 (experiment 4) —Water drinking experiment

Chart 5 (experiment 5) —Water drinking experiment. At A, 2 liters of tap water was given by mouth.

found to be the case with dogs. Unfortunately, in this experiment the greatest depression of the conductivity curve was missed, the second sample of blood being taken after the return to normal had begun. At the end of the experiment, a fifth sample of blood was drawn six minutes after the fourth sample, stasis having been maintained meanwhile. The results show a drop in conductivity and an increase in protein, which is in accord with Dautrebande, Davies and Meakins,⁷ and is what one would expect from Henderson's¹⁰ nomogram, with a rise of carbon dioxide in the tissues.

⁹ Hashimoto, M. Zur Frage der aus dem Verdauungstrakt darstellbaren diuretisch wirkenden Substanz, *Arch f exper Path u Pharm* **76** 367, 1914.

¹⁰ Henderson, L. J., Bock, A. V., Field, H., and Stoddart, J. L. Blood as a Physicochemical System, *J Biol Chem* **59** 379, 1924.

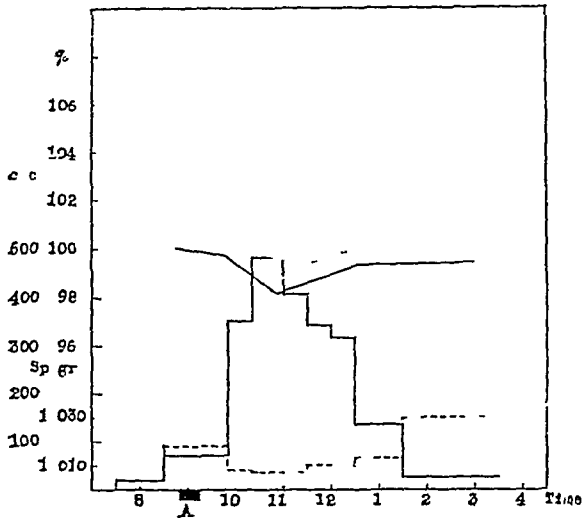


Chart 6

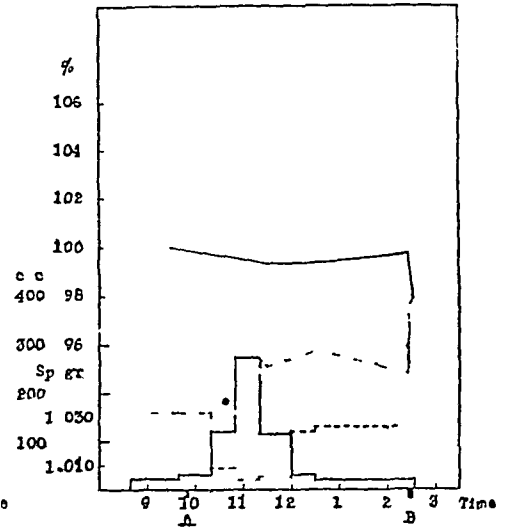


Chart 7

Chart 6 (experiment 6) —Water drinking experiment At *A*, 2 liters of tap water was given by mouth

Chart 7 (experiment 7) —Water drinking experiment At *A*, 700 cc of distilled water was given by mouth At *B*, stasis was maintained for six minutes between the fourth and fifth samples of blood

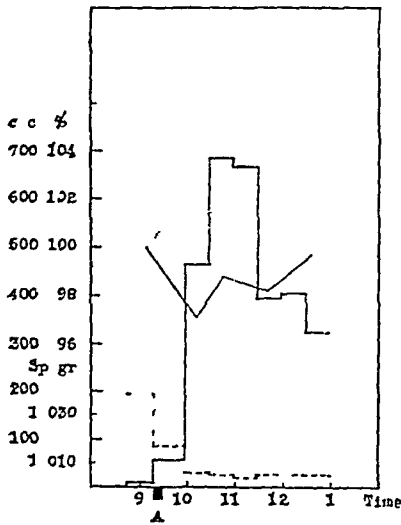


Chart 8

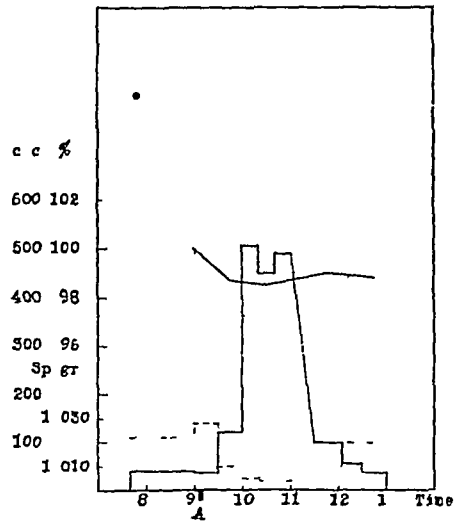


Chart 9

Chart 8 (experiment 8) —Water drinking experiment At *A*, 1,400 cc of tap water was given by mouth

Chart 9 (experiment 9) —Water drinking experiment At *A*, 1 liter of tap water was given by mouth

Protocol of Experiment 4

March 31, 1923		Blood					Urine			
Time	Notes	Specific Con- ductivity	Per Cent	Refrac- tive Index	Per Cent	Vis- cosity	Amt	Rate	Specific Gravity	Specific Con- ductivity
9 00	Blood	0 01198	100	0 0176	100	1 75				
9 01-9 15	2,000 cc tap water by mouth									
9 30	1,000 cc vomited									
9 45	Blood	0 01188	99 2	0 0169	96 1	1 75				
10 50	Urine						360		1 005	
11 00	Blood	0 01181	98 7	0 0174	98 9	1 75				
11 40	Urine						390		1 002	
12 55	Urine						345		1 001	
1 00	Blood	0 01197	100	0 0174	98 9	1 75				

Protocol of Experiment 5

April 2, 1923		Blood					Urine			
Time	Notes	Specific Con ductivity	Per Cent	Refrac tive Index	Per Cent	Vis cosity	Amt	Rate	Specific Gravity	Specific Con ductivity
9 10	Bladder emptied									
9 20	Blood	0 01221	100	0 0167	100	1 73				
9 30-9 45	2,000 cc of tap water by mouth									
10 25	Blood	0 01174	96 2	0 0176	105 3	1 73				
10 35	Urine						140	99		0 01139
11 30	Blood	0 01184	97 0	0 0167	100	1 72				
11 40	Urine						475	439		0 00274
12 10	Urine						280	560		0 00233
12 30	Blood	0 01196	98 0	0 0168	100 6	1 72				
12 40	Urine						235	470		0 00221
1 40	Urine						300	300		0 00235
2 45	Urine						125	115		0 00522
3 10	Blood	0 01193	98 0	0 0172	103	1 72				
4 15	Urine						46	30		0 01518

Protocol of Experiment 6

June 5, 1923		Blood					Urine			
Time	Notes	Specific Con ductivity	Per Cent	Refrac tive Index	Per Cent	Vis- cosity	Amt	Rate	Specific Gravity	Specific Con ductivity
7 30	Bladder emptied									
8 35	Weight, 68,100 Gm									
8 35	Urine						20	20	?	0 026
8 45	Blood	0 012109	100	0 0169	100	1 86				
8 50-9 15	2 000 trip water by mouth									
9 45	Blood	0 012073	99 7	0 0180	106 5	2 00				
9 50	Urine						94	70 5	1 018	0 011
10 20	Urine						175	350	1 008	0 002
10 50	Blood	0 011869	98 1	0 0167	98 9	1 82				
11 00	Urine									
11 30	Urine						320	480	1 007	0 002
12 00	Urine						202	404	1 007	0 002
12 30	Urine						170	340	1 010	0 002
12 32	Blood	0 012017	99 3	0 0169	100	1 87	158	316	1 010	0 002
1 30	Urine									
3 00	Blood	0 012035	99 4	0 0169	100	1 87	135	135	1 013	0 004
3 20	Urine									
3 25	Weight, 67,870 Gm						48	24	1 030	0 019

Protocol of Experiment 7

November 4, 1923		Blood						Urine		
Time	Notes	Specific Con- ductivity	Per Cent	Refrac- tive Index	Per Cent	Pro- tein	Per Cent	Amount	Rate	Specific Gravity
8 40	Bladder emptied									
9 30	Blood	0 01186	100	0 0204	100	8 21	100			
9 40	Urine							22	22	1 032
9 41	Weight, 67,000 Gm									
9 50	700 cc distilled water by mouth									
10 20	Urine							15	30	1 032
10 30	Blood	0 01178	99 3	0 0211	103 4	7 81	95 1	60	120	1 009
10 50	Urine							136	272	1 004
11 20	Urine							77	115	1 005
11 32	Blood	0 01178	99 3	0 0193	91 6	7 86	95 7	15	30	1 024
12 00	Urine									
12 30	Urine									
2 25	Blood	0 01181	99 7	0 0173	84 8	7 78	94 8			
2 31	Blood, after stasis	0 01189	97 8	0 0182	89 2	8 57	101 3	40	10 2	1 026
2 35	Urine									
2 40	Weight, 67,000 Gm									

Protocol of Experiment 8

June 3, 1924		Blood				Urine		
Time	Notes	Specific Conductivity	Per Cent	Pro- tein	Per Cent	Amount	Rate	Specific Gravity
8 46	Bladder emptied							
9 10	Blood	0 01186	100	7 12	100			
9 17	Urine					9	8 5	1 039
9 17-9 27	1,400 cc tap water by mouth							
9 57	Urine					38	57	1 017
10 12	Blood	0 01151	97 1	7 31	102 6	232	464	1 006
10 27	Urine					342	684	1 005
10 43	Blood	0 01172	98 8	7 18	100 8	334	668	1 004
10 57	Urine					197	394	1 005
11 27	Urine					202	404	1 005
11 42	Blood	0 01165	98 2	7 44	104 4			
11 57	Urine							
12 27	Urine							
12 42	Blood	0 01184	99 8	7 35	103 2	162	324	1 005
12 57	Urine							

Protocol of Experiment 9

June 7, 1924		Blood				Urine		
Time	Notes	Specific Conductivity	Per Cent	Pro- tein	Per Cent	Amount	Rate	Specific Gravity
7 40	Bladder emptied							
9 00	Blood	0 01183	100	7 23	100			
9 02	Urine					54	39 5	1 022
9 05-9 10	1,000 cc tap water by mouth							
9 30	Urine					17	36 5	1 028
9 45	Blood	0 01167	98 7	6 90	95 4	61	122	1 010
10 00	Urine					168	504	1 005
10 20	Urine							
10 30	Blood	0 01165	98 5	7 26	100 3	157	449	1 004
10 41	Urine					163	489	1 004
11 01	Urine					—	—	—
11 31	Urine							
11 46	Blood	0 01171	99 0	7 05	97 5	56	99	1 010
12 05	Urine					23	55	1 020
12 30	Urine							
12 45	Blood	0 01169	98 8	7 26	100 3	19	38	1 020
1 00	Urine							

Two experiments (figs 10 and 11) were done in which Locke's solution was taken. The diuresis is similar to a water diuresis, in that there is a sharp rise and fall, but it is much less in amount, and excretion continues for some hours at a rate slightly above normal. The rise in conductivity of the serum may be partly explained by the dilution of the proteins.

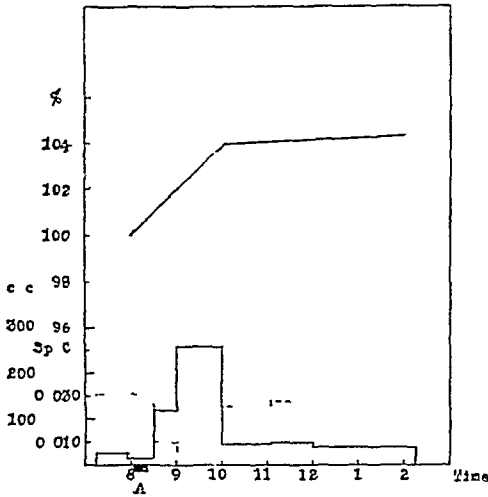


Chart 10

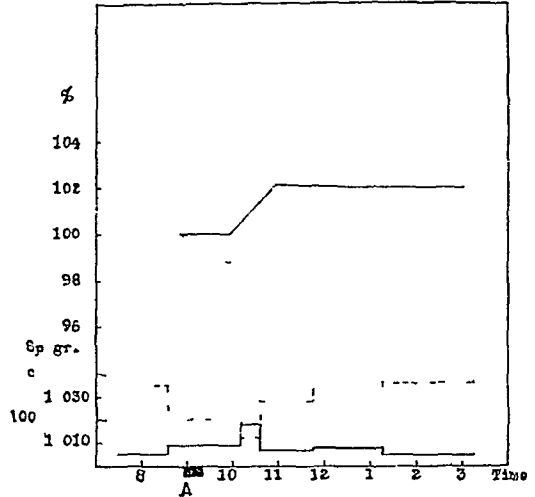


Chart 11

Chart 10 (experiment 10)—Locke's solution experiment. At *A*, 2 liters of Locke's solution was given by mouth.

Chart 11 (experiment 11)—Locke's solution experiment. At *A*, 2 liters of Locke's solution was given by mouth. Specific conductivity of solution 0.0135.

Protocol of Experiment 10

		Blood					Urine			
Time	Notes	Specific Con- ductivity	Per Cent	Refrac- tive Index	Per Cent	Vis- cosity	Amt	Rate	Specific Gravity	Specific Con- ductivity
7 15	Bladder emptied									
7 33	Urine						17	27	—	0.030
8 00	Blood	0.01176	100	0.0170	100	1.77				
8 05-8 20, 2,000 cc Locke's solution by mouth										
8 30	Urine						10	16	—	0.030
8 50	Blood	0.01197	101.7	0.0160	94.2	1.70				
9 00	Urine						60	120	—	0.010
10 00	Urine						260	260	—	0.005
10 05	Blood	0.01214	104.0	0.0162	95.3	1.71				
11 05	Urine						50	46	—	0.026
12 00	Urine						45	49	—	0.028
2 00	Blood	0.01226	104.3	0.0159	93.6	1.70				
2 15	Urine						90	40	—	—

Protocol of Experiment 11

Time	Notes	Blood					Urine		
		Specific Conductivity	Per Cent	Refractive Index	Per Cent	Viscosity	Amount	Rate	Specific Gravity
7 30	Bladder emptied								
8 35	Urine						28	26	1 035
8 40	Weight, 67,750 Gm								
8 50	Blood	0 012179	100	0 0170	100	1 92			
8 55-9 20	2,000 cc Locke's solution by mouth*								
9 55	Blood	0 012179	100	0 0168	98 8	1 86			
10 10	Urine						72	45 5	1 020
10 35	Urine						37	89	1 012
10 55	Blood	0 012428	102 1	0 0161	94 7	1 83			
11 45	Urine						38	32 5	1 028
12 30	Blood	0 012422	102	0 0161	94 7	1 81			
1 15	Urine						56	37 5	1 033
3 00	Blood	0 012422	102	0 0167	98 2	1 82			
3 15	Urine						53	26 5	1 036
3 16	Weight, 68,250 Gm								

* Specific conductivity of Locke's solution, 0 01325 at 25 C

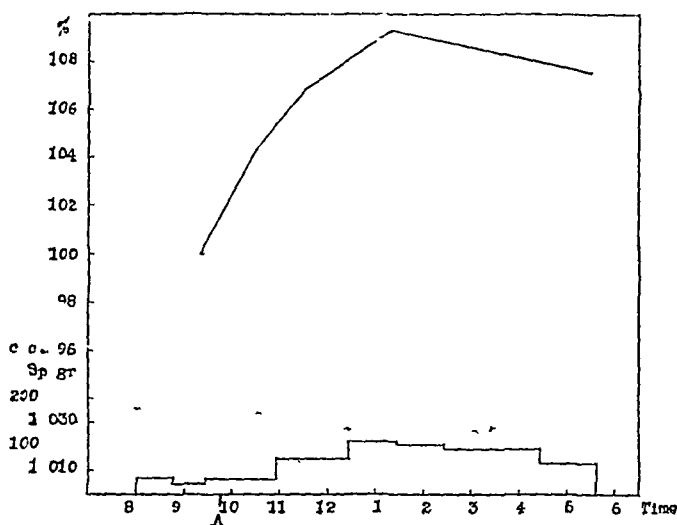


Chart 12 (experiment 12) —Hypertonic salt solution experiment At A, 500 cc of salt solution was given by mouth The solution was composed of 7 per cent sodium chloride, 0 3 per cent potassium chloride, 0 25 per cent calcium chloride, trace, sodium bicarbonate

In one experiment (fig 12), 500 cc of a salt solution of the same composition as Locke's solution, but ten times as concentrated, was taken There was a 9 3 per cent increase in the conductivity, which is only partly explained by the dilution of the proteins The hydremia is probably due to the influx of water from the tissues following the increase in the osmotic pressure of the plasma

Priestley⁶ found that the injection of solution of pituitary following the drinking of water delayed the diuresis for five or six hours,

Protocol of Experiment 12

June 9, 1923		Blood					Urine			
Time	Notes	Specific Con- ductivity	Per Cent	Refrac- tive Index	Per Cent	Vis- cosity	Amt	Rate	Specific Gravity	Specific Con- ductivity
8 00	Bladder emptied									
8 45	Urine						25	33.5	1.036	0.038
8 50	Weight, 68.325 Gm									
9 20	Blood	0.012131	100	0.0172	100	1.82				
9 25	Urine						15	22.5	?	0.039
9 30-9 45	500 cc salt solution by mouth*									
10 30	Blood	0.012659	104.3	0.0172	100	1.81				
10 55	Urine						50	33.5	1.034	0.046
11 30	Blood	0.012956	106.8	0.0163	94.8	1.79				
12 25	Urine						105	73.5	1.028	0.039
1 20	Blood	0.013258	109.3	0.0160	93.0	1.77				
1 25	Urine						110	110	1.027	0.038
2 25	Urine						105	105	1.027	0.041
3 25	Urine						95	95	1.027	
4 25	Urine						95	95	1.028	0.042
5 30	Blood	0.013056	107.6	0.0161	93.6	1.77				
5 35	Urine						75	64.5	1.031	0.043
5 40	Weight, 67.850 Gm									

* The solution was composed of 7 per cent sodium chloride, 0.3 per cent potassium chloride, 0.25 per cent calcium chloride, trace, sodium bicarbonate

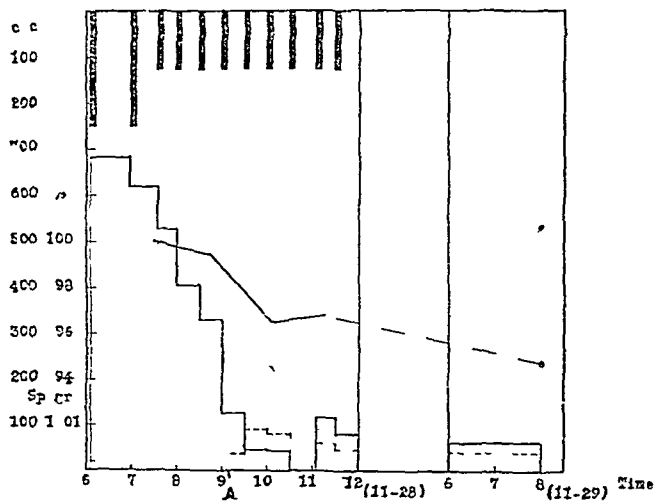


Chart 13 (experiment 13) —Experiment with solution of pituitary in diabetes insipidus. The heavy black areas at the top of the chart indicate cubic centimeters of water by mouth. At A, 0.6 cc of solution of pituitary was given subcutaneously.

but that when it did occur it was normal in amount and rate. Weir¹¹ reviewed the literature on the study of changes in the blood and urine in cases of diabetes insipidus in which solution of pituitary was given, and reported three cases of his own. The prevailing opinion is that the solution of pituitary acts on the kidney cells, causing a retention of water. Experiment 13 (fig 13) was done on a white boy, aged 17,

11 Weir, J. F. Pituitary in Diabetes Insipidus, Arch Int Med 32:617 (Oct) 1923.

who three weeks previously had received a cranial injury in an automobile accident. Following the accident he was unconscious for three days, and twenty-four hours after regaining consciousness he began to complain of great thirst. Since that time, he has had diabetes insipidus with a urine output of from 5 to 10 liters a day. At the time of the experiment, he was on a salt-free diet, which explains the failure of the conductivity of the blood to return to normal on the following day. The dilution of both the electrolytes and the blood proteins would indicate that there was a definite water retention due to a specific action of solution of pituitary on the kidney cells.

Protocol of Experiment 13

Nov 28, 1923								
Time	Notes	Blood				Urine		
		Specific Conductivity	Per Cent	Protein	Per Cent	Amount	Rate	Specific Gravity
6 05	Bladder emptied, 250 cc water							
6 57	Urine					590	681	1 004
6 58	250 cc water							
7 30	Blood	0 01218	100	8 80	100			
7 34	Urine					382	619	1 004
7 35	125 cc water							
8 00	125 cc water Urine					228	526	1 004
8 30	125 cc water Urine					202	404	1 004
8 45	Blood	0 01210	99 4	8 59	97 6			
9 00	125 cc water Urine					165	330	1 005
9 10	0 6 cc solution of pituitary							
9 30	125 cc water Urine					62	124	1 007
10 00	125 cc water Urine					22	44	1 018
10 05	Blood	0 01175	96 5	8 32	94 5			
10 30	125 cc water Urine					21	42	1 016
11 05	125 cc water Urine					0		
11 15	Blood	0 01179	96 8	7 97	91 5			
11 30	125 cc water Urine					48	115	1 012
12 00	Urine					39	78	1 009
Nov 29, 1923								
6 00	Bladder emptied							
8 00	Blood and urine	0 01153	94 7	8 86	100 6	120	60	1 008

* This patient had diabetes insipidus, following a traumatic injury to the head. He was on a salt-free diet, less than 0.5 Gm of salt a day.

RESULTS

The results of the experiments described are in accord with the theory that the osmotic pressure of the plasma is the stimulus of water and salt diuresis. The inaccuracy of the protein determinations is unfortunate, but does not affect the argument, as previous workers have clearly established, that hydremia is absent or is only slight during water diuresis. Priestly found a 2 or 3 per cent increase in water, and there is no reason to suppose that a genuine hydremia may not occur in some cases. The lag of the diuresis following the drop in conductivity shown in some of these experiments is important as indicating that there is probably another factor as well as the osmotic pressure of the plasma concerned with the initiation of a water diuresis. In order to determine this more accurately, more frequent samples of blood should be taken.

than is expedient with the human subject. Also arterial, rather than venous, blood should be used, as small changes in the concentration of the electrolytes are significant. For this reason, large dogs were used as subjects in further experiments. The results, to be published shortly, confirm the observation of a lag in the diuresis after the drop in conductivity of the serum.

SUMMARY

In three control experiments on two subjects, the conductivity of blood from the basilic vein varied from 0.6 to 1.1 per cent during the morning when no food or water was taken.

In six experiments on four subjects, from 700 to 2,000 cc of water was taken by mouth. The conductivity of the blood serum dropped rapidly and rose more slowly. The greatest drop was 3.8 per cent. The diuresis either paralleled the variation of the conductivity or lagged thirty or forty-five minutes behind it. Protein determinations on the blood were unsatisfactory, but in only one case indicated any definite dilution.

In two experiments on one subject, 2,000 cc of Locke's solution was taken. The conductivity increased by 4.3 per cent and 2.1 per cent. The diuresis amounted to 260 cc an hour in one case but only to 45 cc an hour in the other. The dilution of the proteins was fairly definite.

In one experiment, 500 cc of salt solution ten times the concentration of Locke's solution was taken. The conductivity went up nearly 10 per cent. The diuresis did not exceed 110 cc an hour, but was prolonged.

In one experiment in a case of diabetes insipidus following the subcutaneous injection of 0.6 cc of solution of pituitary the conductivity dropped, the proteins were diluted and the diuresis checked, with anuria for one period of thirty minutes.

CHANGES IN THE EYEGROUND IN VASCULAR DISEASES AND IN RELATED CONDITIONS

ONE HUNDRED AND EIGHTY-SEVEN HYPERTHYROID, DIABETIC, NEPHRITIC, HYPERTENSIVE AND CARDIAC CASES, WITH SPECIAL REFERENCE TO RETINAL ARTERIOSCLEROSIS *

HUGO O. ALTNOW, M.D.

MINNEAPOLIS

Contributions to the literature on the study of the eyeground have been numerous, but the majority have been made by ophthalmologists or by internists in collaboration with ophthalmologists. While engaged in the study of vascular diseases at the Peter Bent Brigham Hospital, from February, 1924, to July, 1925, I had an unusual opportunity to study eyegrounds in various vascular diseases and related conditions. Because of the importance that retinal vascular changes have assumed in the diagnosis and interpretation of general vascular disease, I feel that it will be of interest to internists, ophthalmologists and practitioners of medicine to get the point of view of an internist who has had the opportunity to examine a large group of fundi in various diseases. This is a study of eyeground changes and the manner in which they indicate, or reflect, general disorders from the standpoint of one interested chiefly in the problems of internal medicine.

All patients who were admitted consecutively to the medical wards of the Peter Bent Brigham Hospital for an eight months' period (Aug. 1, 1924, to April 1, 1925) with diagnoses of exophthalmic goiter, toxic adenoma of the thyroid, diabetes, acute and subacute nephritis, chronic nephritis, vascular hypertension, chronic myocarditis with and without arrhythmia, cardiac infarction, angina pectoris or chronic cardiac valvular disease were subjected to a thorough study of the eyeground. The ophthalmoscopic examination was made with the pupils dilated, at the same time that blood pressure readings were made, and after the patient had been in bed for several days. The blood pressure readings, therefore, probably represent basal blood pressures. Cases in which diagnoses were doubtful when the patients were discharged from the hospital are not included in this report. The original purpose of this study was to obtain a record of changes in the eyeground in certain groups of vascular and related conditions. In addition, some comments will be made on the clinical aspects of the changes.

* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

* This study was aided by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

In determining the presence of retinal arteriosclerosis, I have adopted as primary evidence of its existence the criteria of O'Hare and Walker¹ I quote their statement

The two signs of arteriosclerosis (retinal) that are absolute and beyond criticism are compression effects at the arteriovenous crossings and irregularity of the lumen (of the arteries)

They feel that the other less important signs are too variable and depend too much on personal judgment to be infallible As secondary evidence of retinal arteriosclerosis, I have accepted, in the order of their importance, the following (1) lack of uniformity in the light streak, particularly when dulled in segments and bright in others, (2) narrowing of the central light streak, especially in branches of the second and third order, (3) loss of translucency (early copper wire artery), (4) narrowing of the whole vessel and (5) tortuosity of two types the corkscrew tortuosity of the macular artery and the "wide-looped" tortuosity of the larger vessels The first four changes are included under departures from the normal in the normal arterial reflex The wide-looped tortuosity is probably due to loss of elasticity and rigidity of the main temporal and nasal arteries These changes are considered by Moore² as indicating retinal arteriosclerosis Typical copper wire arteries, obliteration, beading and calcification take their place together with irregularity of the lumen and arteriovenous compression, as undeniable evidence of retinal arteriosclerosis

In the interpretation and comments on the relation of sclerosis of the retinal vessels to vascular hypertension, I am accepting as my criterion the work of O'Hare and Walker¹ and their observations on sixteen patients with normal or low blood pressures who previously were known to have had hypertension Fourteen patients in this group had definite retinal arteriosclerosis O'Hare and Walker believe that the recurrence of retinal arteriosclerosis indicates the probability of a previous hypertension From my own observations in examining similar cases, I am strongly inclined to verify their opinion This is also in accord with the view held by Fahr,³ who says that so far as his investigations go, definite irregularities of the lumen and arteriovenous compressions are indications of a previous hypertension, even though at the time of examination the blood pressure is within normal limits

1 O'Hare, J P, and Walker, W G Arteriosclerosis and Hypertension, Arch Int Med **33** 343 (March) 1924

2 Moore, R F Retinitis of Arteriosclerosis and Relation to Renal Retinitis and to Cerebral Vascular Disease, Quart J Med **10** 29 (Oct-Jan) 1916-1917

3 Fahr, G E Personal communication to author

The ophthalmoscopic appearance and the changes in the vessels due to sclerosis of the retinal arteries will receive special consideration when I comment on the changes in the cardiac group. In this group the majority of cases showed definitely recognizable vascular changes, usually unaccompanied by any marked retinal edema or retinitis. This made detailed study of these changes possible. However, there is no essential difference in the vascular changes described in this group as compared to those observed in the cases in the other groups in which retinal vascular sclerosis was present.

GROUP I CHANGES IN THE EYEGROUND IN EXOPHTHALMIC GOITER
AND IN TOXIC ADENOMA OF THE THYROID

In the selection of the cases included in table 1, namely, those of exophthalmic goiter and adenoma of the thyroid, only patients with elevated basal metabolic rates were included. As the increased metabolism demands an increased cardiac output, and since increased cardiac output is one factor in producing hypertension and another is increased resistance in the vascular periphery, it seemed desirable to study the retinal vessels in a group of these cases. In exophthalmic goiter, increased cardiac output produces only moderate elevation of the systolic blood pressure, if the pressure is increased at all. The increased cardiac output produces increased pulse pressure, largely by lowering the diastolic blood pressure if the vascular periphery is normal. There can be little doubt that the arterial system undergoes some strain in this adaptation. In toxic adenoma (probably because of the factor of increased age), the diastolic pressure is more likely to be at a fixed level, and in order that the circulation may adapt itself to the increased cardiac output, an elevation in the systolic blood pressure must take place. The increased cardiac output is the result of increased cardiac rate.

The incidence of retinal arteriosclerosis in this group will be commented on with reference to the absence or presence of hypertension,⁴ and not on the basis of the clinical diagnosis, since the diagnosis was not always definite on whether the case was one of exophthalmic goiter or of toxic adenoma. However, out of eleven cases in which the condition was diagnosed as exophthalmic goiter, only four (128, 134, 136 and 139) showed definite retinal arteriosclerosis. In these four, three

4 In this, as well as in the other groups studied, a systolic blood pressure of 145 mm has been arbitrarily chosen as the dividing line between nonhypertensive and hypertensive cases. Patients with a systolic blood pressure within a range of from 145 to 160 are considered to have slight hypertension, while a range of from 160 to 180 indicates moderate hypertension and above 180 marked hypertension. I am aware that many clinicians will consider from 145 to 160 mm a low range to come within the definition of hypertension.

TABLE 1—Changes in the Eyeground in Patients with Exophthalmic Goiter and Adenoma of the Thyroid

Case No	Diagnosis	Age	Blood Pressure	Disks			Retinas			Arteries		Veins			Remarks
				Edema	Increased Vascularity	Hemorrhage or Exudate	Spots	Pigment	Tortuous	Irregular	Arteriosclerosis	Tortuous	Dilatation	Choked Veins	
121	Hyperthyroidism	27	102/68	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
122	Hyperthyroidism	24	112/74	0	0	0	0	0	++	0	0	0	0	0	No retinal arteriosclerosis
123	Exophthalmic goiter	29	116/72	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
124	Exophthalmic goiter with hyperthyroidism	22	118/58	0	0	0	0	0	0	0	+	0	0	0	No retinal arteriosclerosis
125	Exophthalmic goiter with hyperthyroidism	34	128/53	0	0	0	0	0	0	±	++	0	0	0	Doubtful retinal arterio sclerosis
126	Chronic myocardiitis, hyperthyroidism, auricular fibrillation	46	132/80	0	0	0	0	+	++	0	++	0	±	0	Doubtful retinal arterio sclerosis
127	Exophthalmic goiter, hyperthyroidism	15	131/68	0	0	0	0	0	0	0	+	0	0	0	Doubtful retinal arterio sclerosis
128	Exophthalmic goiter, myocardiitis	54	134/68	0	0	0	0	0	0	++	+++	+	0	+	Definite retinal arterio sclerosis
129	Exophthalmic goiter, hyperthyroidism	31	138/74	0	0	0	0	+	+	0	++	0	0	0	No retinal arteriosclerosis
130	Exophthalmic goiter, hyperthyroidism	48	138/82	0	0	0	0	0	0	0	++	0	±	++	Doubtful retinal arterio sclerosis
131	Exophthalmic goiter, hyperthyroidism	46	140/70	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
132	Auricular fibrillation, hyperthyroidism	39	142/76	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
133	Exophthalmic goiter, hyperthyroidism	58	146/0	0	+	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis, pulsation in arteries and veins
134	Exophthalmic goiter, chronic myocardiitis, auricular fibrillation	35	148/60	0	+	0	0	0	0	0	++	0	++	0	Definite retinal arterio sclerosis
135	Exophthalmic goiter, hyperthyroidism	48	152/72	0	0	0	0	0	0	0	+++	0	+	0	Definite retinal arterio sclerosis
136	Exophthalmic goiter, hyperthyroidism, hypertension	52	162/84	0	0	0	0	0	+++	++	+++	0	+	0	Definite retinal arterio sclerosis
137	Adenoma of thyroid, hyperthyroidism	52	168/62	+	+	0	0	0	0	+	+	0	+	++	Definite retinal arterio sclerosis
138	Thyroid adenoma, chronic myocardiitis	61	168/100	0	0	0	0	0	++	+	++	0	0	0	Definite retinal arterio sclerosis
139	Exophthalmic goiter, chronic myocardiitis, auricular fibrillation	59	184/76	0	0	0	0	0	+	0	++	0	0	0	Definite retinal arterio sclerosis
140	Thyroid adenoma, hyperthyroidism, myocardiitis and auricular fibrillation	62	242/130	0	0	0	0	+	++	++	++	0	0	++	Definite retinal arterio sclerosis, grayish white and buff spots, early chorioretinitis

of the patients (128, 136 and 139) were of an age at which the vascular degenerative processes begin to manifest themselves. Three patients (137, 138 and 140) with a condition diagnosed as toxic adenoma showed definite retinal arteriosclerosis. They also fell into the same age group. The incidence of retinal arteriosclerosis in the nonhypertensive and hypertensive patients is shown in table 2.

SUMMARY OF GROUP I

When this group is viewed as a whole and the cases in the sixth decade and older are eliminated, one sees a rather striking absence of retinal arteriosclerosis. This lends support to the idea, expressed later, that retinal arteriosclerosis is secondary to hypertension. This is, to some extent, in accord with the observations of Benedict,⁵ who states

Cardiac stimulation alone is insufficient to produce vascular sclerosis, even with the presence of long-continued high blood pressure, is the conclusion reached after the study of exophthalmic goiter.

TABLE 2—*Retinal Arteriosclerosis in Group I*

	Definite, Percentage	Doubtful, Percentage	None, Percentage
Without hypertension	8.3	25.0	66.7
With hypertension	87.5	0.0	12.5

GROUP II CHANGES IN THE EYEGROUND IN DIABETES

The changes in the eyegrounds of forty-seven diabetic patients of all ages (children under 12 years excluded) are included in table 3. The frequency of the occurrence of retinal arteriosclerosis is shown in table 4.

SUMMARY OF GROUP II

In the nonhypertensive and hypertensive groups together, the incidence of retinal arteriosclerosis was 42.5 per cent. According to the criteria adopted in the interpretations in this study, it would mean that this many patients probably had hypertension prior to, or during, the diabetes. O'Hare and Walker⁶ suggest that hypertension may play an important part in the etiology of diabetes in elderly persons, and that hypertension, instead of terminating in cerebral arteriosclerosis, cardiac failure or chronic nephritis, may terminate in diabetes. O'Hare,⁷ in a study of the dextrose tolerance of patients with hypertension, has

⁵ Benedict, W. L. Retinitis of Hypertension, American Medicine, new series, **17** 467 (June) 1923.

⁶ O'Hare, J. P., and Walker, W. G. Heart in Hypertension, Boston M. & S. J. **190** 683 (April 24) 1924.

⁷ O'Hare, J. P. Glucose Tolerance Test in Chronic Vascular Hypertension, Am. J. M. Sc. **160** 966, 1920.

TABLE 3—Changes in Eyeground in Forty-Seven Patients with Diabetes

Case No	Diagnosis	Age	Blood Pressure	Disks			Retinas			Arteries			Veins			Remarks	
				Increased Hem- Vascul- larity			Hem- or rhage			Tor- tuous	Irreg- u- lar	Arterio- sclero- sis	Tor- tuous	Disten- sion	Papill- edema		Choked Veins
				Edema	larity	rhage	Edema	rhage	Spots								
111	Diabetes 6 months	26	80/52	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis	
112	Diabetes 7 months	35	90/72	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis	
113	Diabetes 3 years	13	98/63	±	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis, retinas red	
114	Diabetes 1 month	10	98/60	0	0	0	0	0	0	0	++	+	0	0	+	No retinal arteriosclerosis	
115	Diabetes, secondary anemia 1½ years	13	98/52	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis	
116	Diabetes 3 years	11	98/61	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis	
117	Diabetes 5 years	36	102/60	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis, nonmedullated nerve fibers	
118	Acidosis, diabetes 1 year	17	102/53	0	0	0	0	0	0	0	++	0	0	0	0	No retinal arteriosclerosis	
119	Diabetes 4½ years	47	104/76	0	0	0	0	0	0	±	++	0	0	±	0	Doubtful retinal arterio-sclerosis	
120	Diabetes, pulmonary tuberculosis 3 years	20	106/56	0	0	0	0	0	0	+	0	0	0	0	0	No retinal arteriosclerosis	
121	Diabetes arterio-sclerosis 3 months	16	106/76	0	0	0	0	0	0	0	0	+	0	0	+	No retinal arteriosclerosis	
122	Diabetes 1 year	33	106/52	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis, retinas red	
123	Diabetes 2 years	20	108/81	0	0	0	0	0	0	0	+	0	0	0	0	No retinal arteriosclerosis	
124	Diabetes, arterio-sclerosis 8 to 10 years	60	112/86	0	Pallor	0	0	0	0	0	+++	0	0	0	++	Definite retinal arterio-sclerosis, advanced chorioretinitis, contracted vessels	
125	Diabetes 1 year	26	114/66	0	0	0	0	0	0	0	0	0	0	0	+	No retinal arteriosclerosis	
126	Diabetes 3 years	31	114/72	0	0	0	0	0	0	0	0	+	0	0	+	No retinal arteriosclerosis	
127	Diabetes, arterio-sclerosis 5 years	71	116/78	++	0	0	0	+	++++	0	+++	++	++	+++	+++	Definite retinal arterio-sclerosis, old papill edema, with secondary optic atrophy, superficial hemorrhages, numerous grayish white spots, sheathing of vessels	
128	Diabetes with coma, pulmonary tuberculosis 2 years	42	122/76	0	0	0	0	0	0	0	+	0	0	0	0	No retinal arteriosclerosis	

159	Diabetes, syphilis diabetic cataract 4 years	50	122/76	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	No retinal arteriosclerosis, beginning cataract in the left eye
160	Diabetes 6 months	52	124/70	See note	0	0	0	0	0	0	0	0	0	0	0	0	±	++	Doubtful retinal arterio- sclerosis, conus tempor- alis, edge of disk has "fuzzy" appearance
161	Diabetes, myocar- ditis, adhesive pericarditis?	54	126/68	±	0	0	0	0	0	0	0	0	+	++	0	0	0	++	Definite retinal arterio- sclerosis, small round hemorrhages
162	Diabetes, hyper- tension 1 year	47	128/84	0	0	0	0	0	0	0	0	++	+	++	0	0	++	+	Definite retinal arterio- sclerosis, rejected 1 year ago for insurance on account of hypertension
163	Diabetes hyper- tension?	62	128/76	0	0	0	0	++	++	++	0	0	0	0	0	0	++	⊕	Definite retinal arterio- sclerosis, small round and large superficial hemorrhages, finely pen- ciled macular fan, "dia- betic retinitis"
164	Diabetes 3 months	50	128/74	0	0	0	0	+	++	++	0	++	0	++	0	0	+	0	Doubtful retinal arterio- sclerosis, small round hemorrhages, buff and small white spots
165	Diabetes, tumor of the brain?	52	130/85	+	0	0	0	0	0	0	0	++	±	++	+	0	++	0	Definite retinal arterio- sclerosis
166	Diabetes 4 to 5 years	46	132/78	0	0	0	0	++	0	0	0	++	+	++	++	++	++	+	Definite retinal arterio- sclerosis, small, round hemorrhages
167	Diabetes, primary anemia, tumor of the cord?	61	132/66	0	0	0	0	0	0	0	0	0	±	++	0	0	0	0	Doubtful retinal arterio- sclerosis
168	Diabetes, colitis, 1 year	58	130/0	0	0	0	0	0	0	0	0	0	+	++	0	0	0	0	Doubtful retinal arterio- sclerosis
169	Diabetes?	63	136/96	0	0	0	0	0	0	0	0	0	±	++	0	+	+	+	Definite retinal arterio- sclerosis
170	Diabetes, obesity?	60	138/88	0	0	0	0	0	0	0	0	+	0	0	0	0	++	++	Definite retinal arterio- sclerosis
171	Diabetes?	60	138/82	0	0	0	0	0	0	+	0	+	++	++	0	0	++	0	Definite retinal arterio- sclerosis, buff spots
172	Diabetes, arterio- sclerosis 8 years	42	138/82	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	No retinal arteriosclerosis
173	Diabetes, arterio- sclerosis 20 years	62	144/82	0	0	0	0	+	++	++	0	++	++	++	0	0	++	0	Definite retinal arterio- sclerosis, buff spots, small, round hemor- rhages
174	Diabetes 8 years	60	144/82	0	0	0	0	++	++	++	0	+	±	++	0	0	++	0	Definite retinal arterio- sclerosis, beginning "dia- betic retinitis"

TABLE 3—Changes in Eyeground in Forty-Seven Patients with Diabetes—Continued

Case No	Diagnosis	Age	Blood Pressure	Disks			Retinas			Arteries		Veins		Remarks
				Edema	Increased Vascularity	Hemorrhage	Spots	Pigment	Toruous	Irregular	Arteriosclerosis	Toruous	Dilatation	
175	Diabetes, arterio sclerosis 7 to 8 years	64	144/60	0	0	0	0	0	0	++	+++	0	0	Definite retinal arterio sclerosis
176	Diabetes, obesity 5 years	51	141/90	0	0	0	++	0	0	++	+++	0	0	Definite retinal arterio sclerosis, cataract in the left eye, small superficial hemorrhages, beginning "diabetic retinitis" macular fan
177	Diabetes ?	43	146/82	0	0	0	0	0	0	++	+	0	0	Definite retinal arterio sclerosis, nonmedullated nerve fibers
178	Diabetes 2 years	57	152/96	0	0	0	0	+	+	+++	++	0	++	Definite retinal arterio sclerosis
179	Diabetes, arterio sclerosis 6 years	54	156/78	0	0	0	0	0	+	+++	++	0	0	Definite retinal arterio sclerosis, beginning bilateral cataract
180	Diabetes ?	52	156/80	0	0	0	0	0	0	0	++	0	0	No retinal arteriosclerosis
181	Diabetes 1 year	44	138/96	0	0	0	0	0	+++	+	++	0	0	Definite retinal arterio sclerosis, small, round hemorrhages
181	Diabetes 9 years	44	158/96	±	0	0	0	0	0	+	+	0	0	Definite retinal arterio sclerosis
183	Diabetes, arterio sclerosis 3 to 4 years	63	162/88	0	0	0	++	+	++	0	++	0	0	Definite retinal arterio sclerosis, "diabetic retinitis," small, round hemorrhages, yellowish white spots
184	Diabetes ?	60	171/96	0	0	0	0	0	0	++	+++	0	0	Definite retinal arterio sclerosis
185	Diabetes, myocarditis and hypertension 11 years	56	192/108	0	+	0	0	0	0	+	0	0	0	Definite retinal arterio sclerosis, retinas red and hazy
186	Diabetes 11 years	53	106/102	0	0	0	0	0	0	+	+	++	0	Doubtful retinal arterio sclerosis
187	Diabetes, arterio sclerosis 1 year	63	214/98	0	0	0	++	0	0	+	++	0	0	Definite retinal arterio sclerosis, large, round hemorrhages

found that a large majority exhibit a diabetic curve. He suggests that all patients with hypertension are at least potentially diabetic patients, and that sclerosis of the vessels of the pancreas with resulting insufficiency of the islands is the probable explanation for the increase in blood sugar.

In the group examined in this study, the average age of diabetic patients with definite retinal arteriosclerosis was 57.5 years, while in those showing doubtful or no retinal arteriosclerosis, the average age was 33. Definite or doubtful arteriosclerosis did not occur in any patient under 30 years of age. If the presence of retinal arteriosclerosis is a sign of sclerosis of small vessels in other parts of the body, this appears to indicate that sclerosis of small vessels may be a factor in the production of diabetes after 50 years of age, it is, at least, a common occurrence. Sclerosis of the small vessels does not appear to be a necessary factor in the production of diabetes in the young person. Some degree of sclerosis of the choroidal vessels and chorioretinitis was present in 40 per cent of the cases. Adam⁸ mentions diabetes as an

TABLE 4—*Retinal Arteriosclerosis in Group II*

	Definite, Percentage	Doubtful, Percentage	None, Percentage
Without hypertension	31.6	13.9	50.0
With hypertension	81.8	9.1	9.1

occasional cause of this condition, it is found with greater frequency in the diabetic group than in the other groups included in this series.

Changes in the disk were infrequent as compared with changes in the eyeground in hypertension and nephritis, only two cases showing definite papilledema. There were other causes for the changes in the disk observed in the series of diabetic cases. In case 157, there was an old papilledema with secondary atrophy, accompanied by marked vascular sclerosis and retinal change, while in case 165 there was a question of tumor of the brain associated with the diabetes. Shafer⁹ and Grafe¹⁰ both comment on the absence or infrequency of papilledema in diabetes.

Not counting small deposits of pigment, eleven of forty-seven cases of diabetes showed some abnormal retinal changes. Eight cases showed small, round hemorrhages in the deeper layers of the retinas, in one instance, case 187, there was a single, large, round hemorrhage. In contrast to this, only two cases showed superficial flame-shaped or

⁸ Adam, Curt. *Ophthalmoscopic Diagnosis*, Berlin, 1913, trans. by Matthias L. Foster, New York, Rodman Co., 1913, 229 pp., 48 pl.

⁹ Shafer, J. J. *Diabetic Retinitis*, *Am J Surg* **32**: 67 (March) 1918.

¹⁰ Volhard, quoted by Grafe, E. *Changes of the Retinae in Diabetes*, *Klin Wchnschr* **2**: 1216 (June 25) 1923.

irregular hemorrhages Four cases (163, 174, 176 and 183) showed small yellowish-white spots or macular fan formation (or incomplete macular star) in the central portion of the retinas This type of retinitis, together with small, round hemorrhages, is considered by many observers as characteristic of "diabetic retinitis" In two cases, 163 and 176, there was beginning fan formation In every instance, the patients who had retinitis were above 40 years of age and had definite retinal arteriosclerosis Three had a systolic blood pressure above 145 mm at the time of examination

There is some diversity of opinion as to whether or not diabetes in itself produces characteristic retinal changes Wagener and Wilder¹¹ state that retinitis does not occur in uncomplicated diabetes Volhard (quoted by Grafe¹⁰) says that he has never seen diabetic retinitis when it was not associated with hypertension Garrod¹² states that diabetic retinitis occurs only in elderly patients, while Bardsley¹³ calls attention to two cases seen by him in patients 26 and 35 years of age The first patient had a normal blood pressure

The prevailing opinion, and probably the correct one, is that expressed by Garrod,¹² Friedenwald,¹⁴ Grafe¹⁰ and Wagener,¹¹ that vascular change and hypertension are the factors of primary importance in the production of diabetic retinitis, while hyperglycemia and metabolic disturbance are of secondary importance and responsible for the individual characteristics

From the visual impressions that I have retained after examining this group of diabetic patients, I would say that the following appearances suggest diabetic retinitis (1) a retina that is redder than normal, with a brilliant arterial reflex, (2) the presence of small, round hemorrhages which appear through the ophthalmoscope to be from 1 to 2 mm in diameter, (3) small, discrete, yellowish-white and grayish-white spots seen in groups on the central field of the retina, (4) fan formation, (5) retinal arteriosclerosis with disks that appear normal or nearly normal, and (6) some degree of sclerosis of the choroidal vessels in the periphery

GROUP III OBSERVATIONS ON THE EYEGROUND IN ACUTE AND IN SUBACUTE NEPHRITIS

The opportunity to examine a large number of patients with acute and subacute nephritis did not present itself during the period of study, because a majority of the patients in the medical wards had reached

11 Wagener, H P, and Wilder, R M Retinitis of Diabetes Mellitus, J A M A **76** 515 (Feb 19) 1921

12 Garrod, Sir Archibald Diabetes in Relation to Diseases of the Eye, Arch Ophth **1** 378 (July) 1921

13 Bardsley, P C Ibid, p 384 (Discussion of Garrod's paper)

14 Friedenwald, H Diabetic Retinitis, J A M A **85** 428 (Aug 8) 1925

TABLE 5—Changes in the Eyeground in Nine Cases of Subacute Nephritis

Case No	Diagnosis	Age	Blood Pressure	Disks			Retinas			Arteries			Veins			Remarks	
				Edema	Vascularity	Hemorrhage	Edema	Hemorrhage	Spots	Pigment	Tortuous	Irregular	Arteriosclerosis	Tortuous	Dilatation		Papill-Choked Veins
72	Acute hemorrhagic nephritis	13	118/72	0	0	0	0	0	0	0	0	++	0	0	0	No retinal arteriosclerosis, bright red arteries probably normal for age	
73	Acute nephritis	18	154/94	0	0	0	0	0	0	0	0	0	0	0	+	No retinal arteriosclerosis	
74	Subacute nephritis	30	106/78	0	0	0	0	0	0	0	0	+	+	0	0	No retinal arteriosclerosis	
75	Subacute nephritis	46	103/78	0	0	0	0	0	+	0	0	0	++	0	0	No retinal arteriosclerosis, buff spots	
76	Subacute nephritis with edema	43	115/80	+	0	0	+	0	0	0	++	++	++	+	++	Definite retinal arterio sclerosis	
77	Subacute nephritis	13	128/66	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis	
78	Subacute hemorrhagic nephritis	16	132/86	0	0	0	0	0	0	+	0	±	++	0	0	Doubtful retinal arterio sclerosis	
79	Subacute nephritis	38	134/78	++	+	+	+	0	+++	+	+	++	+++	+	++	Definite retinal arterio sclerosis, cotton and soft grayish white spots	
80	Subacute nephritis with edema, renal insufficiency	20	160/92	0	0	0	++	++++	+	0	0	++	++	0	0	Definite retinal arterio sclerosis, flame shape hemorrhages, gray white and hard white spots	

an age when acute nephritis is rather uncommon. However, nine cases were studied, and the results are given in table 5. Three patients showed definite arteriosclerosis, including two patients with definite hypertension. Case 76 is interesting because the patient always had a normal or low blood pressure during the long period that he was under observation. He also had marked albuminuria with a large number of fatty casts and marked edema, a low basal metabolism and a practically normal renal function, except for a slightly diminished phthalein output. Clinically, his condition resembled nephrosis. It was difficult to explain his retinal arteriosclerosis. Later inquiry into his previous medical history, however, revealed the fact that prior to his admission to the Peter Bent Brigham Hospital he had twice been a patient in the Massachusetts General Hospital on account of hypertension. His record there showed that his blood pressure readings varied between 130

TABLE 6—Summary of Changes in Eyegrounds in Groups IV and V

	Chronic Nephritis 20 Cases	Vascular Hypertension 20 Cases
Disk papilledema	15	10
Increased vascularity	14	6
Hemorrhage	1	1
Retinal edema	14	4
Hemorrhages	16	9
Buff, gray white, yellowish white and white spots, powdery spots	12	11
Cotton wool spots	4	3
Macular fan or star	8	2
Definite retinal arteriosclerosis	13	17
Sclerosis of choroidal vessels	6	6
Examination of vessels unsatisfactory because of retinal edema, high refractive error, etc	3	2
Arteriosclerotic change in macula	2	0
Retinal detachment	2	0

systolic and 80 diastolic and 170 systolic and 110 diastolic. Since I left the Peter Bent Brigham Hospital, this patient has undergone a decapsulation operation. Dr. O'Hare, in a recent communication, states that a biopsy specimen removed at operation showed nephrosis with glomerulitis.

With the exception of one patient with slight papilledema and retinal edema, the retinal changes in patients with nonhypertensive nephritis were negligible. Retinitis was present in only two cases (79 and 30), both patients had hypertension.

GROUPS IV AND V CHANGES IN THE EYEGROUND IN CHRONIC NEPHRITIS AND IN VASCULAR HYPERTENSION

The changes in the cases of the patients with chronic nephritis and vascular hypertension are interesting when compared with one another. A summary of the important changes is seen in table 6. Before commenting on the changes, perhaps I should mention that the majority of these patients had either severe nephritis or severe hypertension and

were admitted to the hospital because they showed symptoms which made us feel that it was not safe to allow them to continue as ambulatory patients. Their condition, therefore, was usually of long standing.

A study of the tables shows that the incidence of papilledema, retinal edema, hemorrhage, macular fan and star formations, arteriosclerotic degeneration in the macular region and retinal detachment was greater in patients with chronic nephritis than in those with hypertension.

Two views are held concerning the production of papilledema in nephritis and hypertension. Larsson¹⁵ believes that it is a manifestation of increased intracranial pressure. He cites the cases of eleven patients with papilledema, all of whom had an increased cerebrospinal fluid pressure, varying from 200 to 600 mm. In two of five cases in which spinal drainage was performed, there was temporary improvement in vision and choking was less marked, in the other cases, there was no improvement, or the visual impairment was increased. Larsson quotes von Hippel's statement that increased lumbar pressure is necessary in choked disk, and that it practically does not exist in the absence of it. Volhard¹⁶ states that the whole picture of nephritis "neuroretinitis" can be explained on the basis of arterial ischemia.

Moore² considers edema of the disk and the secondary atrophy due to disease of the vessels and their inability to transmit an efficient supply of blood.

I cannot express an opinion as to which of the foregoing two factors is operative in the production of papilledema. Spinal drainage was resorted to in case 88. The choking was marked, and long hemorrhages were radially arranged around the disk, not unlike the petals of the dahlia. Daily observation of the eyeground did not show any change in the retinal edema and papilledema after the lumbar puncture, and the patient's condition became definitely worse. For this reason, there was some hesitation in the further application of this method as a therapeutic procedure.

In commenting on the retinal changes that take place as a result of nephritis, I adhere purposely to the somewhat nondescript designation of "spots," instead of referring to them as retinal exudates. With the exception of cotton wool spots, the retinal changes are probably due to a fatty or hyaline degenerative process or in some instances of colloid deposits.

Moore¹⁷ states that pathologic processes of the most diverse origin will produce white spots or areas in the retina. Adam⁸ is of essentially

15 Larsson, S. W. Choked Disc in Nephritis, *Acta Ophth.* **1** 193, 1924.

16 Volhard. Die doppelseitigen hamatogenen Nierenerkrankungen, Staehelin, *Handbuch der inneren Medizin* **3**:2, 1918, quoted by Larsson (footnote 14).

17 Moore, R. F. *Medical Ophthalmology*, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1922, p. 178.

the same opinion concerning their origin, but also believes that fatty degeneration is the principal cause. Semple¹⁸ and Duvigneaud¹⁹ consider cotton wool spots to be, at least at the time of their appearance, a network of fibinous exudate. Moore² has found cotton wool spots, particularly in those cases in which the toxic element of nephritis is prominent. The various degenerative spots are most probably due to ischemia of portions of the retina following changes in the retinal vessels which result in a diminished vascular supply, the cotton wool spots, if caused by a toxic element, may be due to exudation resulting from the action of the toxin on the endothelial lining of the retinal capillaries.

While the significance of the buff spot is not understood, the fact that it was observed with greater frequency than the other varieties of spots and that it also occurred when no other spots were present may indicate that it is the forerunner or any early stage of the other degenerative spots. However, I have not seen these buff spots actually change to gray-white or white spots. The fine "powdery" white spots, or exudate as termed by Moore, were seen in cases 86, 90 and 91. He interprets their presence as indicating a subsidence of the retinitis.² He reports a case in which there was a complete disappearance of the retinitis when the patient was examined seven and one-half years later, at the time of death, which was due to the development of uremia. He believes that retinitis is a self-limited condition, and that a patient who has once had retinitis is protected against further recrudescence.

Tresilian²⁰ also reports a case of a boy, aged 15, who had subacute nephritis, edema, marked albuminuria, papilledema and albuminuric retinitis with macular fan when this author first saw him. Tresilian did not see the patient again until six years later, at the time of his death from uremia. Retinitis was not present nor was there any record of the blood pressure or blood chemistry.

When I examined the patient in case 86 nine months later, the "powdery" white spots and well developed fan had almost completely disappeared.

Cotton wool spots were found in three cases of hypertension (107, 109 and 116). The patient in case 109 developed a sudden renal insufficiency and died about six weeks later. At the time of his retinal

18 Semple, N. M. Some Questions Concerning the Method of Development and the Pathology of the Retinitis of Bright's Disease, *Am Path Soc.* **12** 817, 1909-1911.

19 Rochon-Duvigneaud. Albuminuric Retinitis, *Ophth Rev* **31** 307, 1912, quoted by Benedict (footnote 22).

20 Tresilian, F. Albuminuric Retinitis as a Prognostic Sign, *Brit M J* **1** 148 (Jan 27) 1923.

examination, he had normal renal function. At present it is not possible to trace the fate of the other two patients.

In five of eight cases of chronic nephritis in which a macular star or fan was seen, my notes state that it was coarse, in the other three, its appearance was not noted, in vascular hypertension, the fan was described as fine in one instance, in the other, no special note was made. Moore² states that in arteriosclerotic retinitis and renal retinitis, the star or fan may be present in either case, but that in the former the star is composed of small dots, while in the latter the dots are larger, less discrete and tend to coalesce and form jagged and irregular rods, with edema usually present. My impressions, gathered from further observations, lead me to believe that the lines in the star or fan, when it is present in vascular hypertension, are likely to be more finely "penciled." While in the individual case it may be impossible to tell whether nephritis exists in a patient with hypertension, examination of the eyeground will reveal certain changes which occur with greater incidence when nephritis is present, as is brought out in tables 7 and 8. When one takes into consideration the fact that the group of patients with nephritis includes two with normal tension and that the condition of the vessels was more difficult to determine, particularly because of more marked retinal edema, it will be seen that the incidence of retinal arteriosclerosis is about the same. When there are only one or two definite venous compressions, or the irregularity of lumen is confined to one or two vessels, retinal arteriosclerosis may, under these conditions, easily be overlooked. It is Moore's opinion² that vascular disease is less of a feature in renal retinitis. Only one patient (case 99) showed definite phlebosclerosis. Sclerosis of the choroidal vessels was observed in six cases in which hypertension and nephritis, were also present. With two exceptions, it occurred in association with definite retinal arteriosclerosis.

Arteriosclerotic changes in the macula with a collection of buff spots and later retinal degeneration with pigmentation were observed in three cases of nephritis, namely, cases 84, 94 and 100. Adam⁸ believes that the spots are due to a colloid deposit and later, degeneration produced by vascular change in the blood supply of the macula. This is usually supposed to be a senile change, but in cases 84 and 100 the patients were 36 and 37 years of age.

In cases 90 and 99, the patients exhibited detachment of the retina. "Guttate" choroiditis, showing isolated collections of yellow spots, was seen in one case (106), the patient was 65 years of age. This is considered to be a senile change.

My impression concerning retinitis in hypertension and nephritis is that while the underlying cause is the same, namely, vascular change, the more rapid rate of progression in the retinitis of nephritis is probably

TABLE 7—Changes in the Eyeground in Cases of Nephritis and Vascular Hypertension

Case No	Diagnosis	Age	Blood Pressure	Disks			Retinas			Arteries		Veins		Remarks
				Edema	Increased Vascularity	Hemorrhage or Vaseculopathy	Edema	Hemorrhage	Spots	Pigment	Tortuous	Irregular	Arteriosclerosis	
Case No	Diagnosis	Age	Blood Pressure	Edema	Increased Vascularity	Hemorrhage or Vaseculopathy	Edema	Hemorrhage	Spots	Pigment	Tortuous	Irregular	Arteriosclerosis	Remarks
81	Chronic nephritis with edema	18	110/78	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
82	Chronic nephritis with edema	62	126/78	0	0	0	0	0	++	+	0	+	++	Doubtful retinal arteriosclerosis, grayish white and buff spots
83	Chronic nephritis with edema	20	165/90	++	+	0	+	+	++	0	0	+	++	Doubtful retinal arteriosclerosis, superficial hemorrhages, white spots above macula
84	Chronic nephritis, hypertension	36	166/124	+++	+	0	+++	++	++	0	++	+++	++	Definite retinal arteriosclerosis, many superficial hemorrhages, cotton wool, grayish-white and buff spots about macula
85	Chronic nephritis, uremia	60	180/104	0	0	0	0	0	++	++	0	++	+++	Definite retinal arteriosclerosis, extensive chorioretinitis
86	Chronic nephritis, hypertension	32	192/18	0	0	0	0	0	+++	0	—	—	—	Well developed macular and "powdery" white spots, largely disappeared after 9 months, high degree myopia, examination of vessels unsatisfactory
87	Chronic nephritis with edema, hypertension	23	196/114	+++	++	0	++	++	++	+	0	+++	++	Definite retinal arteriosclerosis, superficial hemorrhages, cotton wool and grayish white spots
88	Chronic nephritis with edema, hypertension	57	198/104	++	+	++	++	++	++	0	0	++	++	Definite retinal arteriosclerosis, "dahlia" retinal spots
89	Chronic nephritis with edema, hypertension	34	204/120	+++	+	0	+++	++	+++	0	+++	0	+++	Definite retinal arteriosclerosis, large subhyaloid "boat shaped" hemorrhages, coarse macular striae

90	Chronic nephritis, hypertension	23	203/114	++	++	0	0	++	++	+	—	—	+	+	—	0	Detachment of retinas, due to marked edema, coarse macular star, "powdery," white spots
91	Chronic nephritis, hypertension	50	210/106	+	0	0	0	++	+++	0	++	0	0	++	++	0	Definite retinal arterio-sclerosis, superficial hemorrhages, cotton wool and "powdery" white spots, copper wire arteries
92	Chronic nephritis	44	216/34	+	0	0	0	++	+++	++	++	++	+	0	++	+	Definite retinal arterio-sclerosis, cotton wool spots and macular fan
93	Chronic nephritis with edema	39	224/138	+	+	0	0	++	0	0	++	+	++	0	++	0	Doubtful retinal arterio-sclerosis, flame shaped hemorrhages
94	Chronic nephritis, hypertension	57	232/140	+++	+	0	0	++	++	++	++	++	++	0	++	0	Definite retinal arterio-sclerosis, flame shaped hemorrhages, beginning choroiditis, macular region
95	Chronic nephritis with edema, hypertension	50	232/144	+++	++	+	0	++	++	0	+	—	—	—	+	0	Superficial hemorrhages, cotton spots, coarse macular star, vessels could not be seen satis- factorily on account of edema
96	Chronic nephritis, uremia, hyper- tension	47	234/110	++	++	0	0	++	+++	0	0	++	++	0	0	+	Definite retinal arterio-sclerosis, macular fan
97	Chronic nephritis, hypertension	54	234/136	+++	++	0	0	++	0	0	+	++	++	++	+	++	Definite retinal arterio-sclerosis, marked phlebo-sclerosis
98	Chronic nephritis, hypertension	39	234/154	0	+	0	0	++	++	0	++	++	++	0	++	0	Definite retinal arterio-sclerosis, macular fan, dagger hemorrhages, copper wire arteries
99	Chronic nephritis, hypertension	49	254/156	+++	++	0	0	++	++	++	++	++	+	++	++	++	Definite retinal arterio-sclerosis, detached retina, coarse macular star, phlebosclerosis
100	Chronic nephritis, hypertension	37	272/160	+++	++	0	0	++	++	++	++	++	++	++	++	0	Definite retinal arterio-sclerosis, choroiditis macular region

TABLE 8—Changes in the Eyeground in Cases of Nephritis and Hypertension

Case No	Diagnosis	Age	Blood Pressure	Disks			Retinas			Arteries			Veins			Remarks
				Edema	Increased Vascularity	Hemorrhage	Edema	Hemorrhage	Spots	Pigment	Tortuous	Irregular	Arteriosclerosis	Tortuous	Dilatation	
101	Hypertension, arteriosclerosis	62	152/80	0	0	0	0	0	++	+	+++	0	0	+	++	Doubtful retinal arterio-sclerosis, buff and grayish white spots
102	Hypertension, chronic bronchitis	55	164/88	0	+	0	0	0	0	++	+++	0	++	+	0	Definite retinal arterio-sclerosis
103	Hypertension, arteriosclerosis	42	170/110	0	0	0	0	0	0	+++	+++	0	0	++	++	Definite retinal arterio-sclerosis
104	Hypertension, arteriosclerosis	53	174/118	0	0	0	0	0	0	+++	++	0	0	++	0	Definite retinal arterio-sclerosis
105	Hypertension, arteriosclerosis, myocarditis	54	182/84	+	+	0	0	+	0	++	++	++	++	+++	++	Definite retinal arterio-sclerosis
106	Hypertension, arteriosclerosis	65	186/88	0	0	0	0	0	+++	++	+++	0	++	++	0	Definite retinal arterio-sclerosis, guttate choroiditis
107	Hypertension, angina pectoris, arteriosclerosis	51	188/108	+	0	0	+	+++	+++	+	+++	0	++	+++	0	Definite retinal arterio-sclerosis, superficial hemorrhages, cotton wool spots and grayish-white spots
108	Hypertension, chronic myocarditis	39	196/128	0	0	0	0	0	+	++	++	0	0	++	0	Definite retinal arterio-sclerosis, buff spots, copper wire arteries
109	Hypertension, perianteritis nodosa	22	208/130	++	+	+	+++	++	+++	—	+++	0	+++	0	0	Superficial hemorrhages, cotton wool spots and fan, examination of vessels unsatisfactory on account of retinal edema

110	Hypertension, myocarditis, retinal arteriosclerosis	59	208/146	+	0	0	0	0	0	+++	+	0	0	+++	+++	Definite retinal arterio- sclerosis
111	Hypertension, arteriosclerosis	74	216/88	0	0	0	0	0	0	++	+++	0	++	++	0	Definite retinal arterio- sclerosis
112	Hypertension myocarditis,	56	218/88	0	0	0	0	0	++	++	++	0	0	++	0	Definite retinal arterio- sclerosis, copper wire arteries
113	Hypertension, arteriosclerosis	55	222/108	0	0	0	0	++	++	++	+++	0	0	+++	0	Definite retinal arterio sclerosis, buff spots
114	Hypertension, myocarditis	60	232/122	+	+	0	0	+	++	++	+++	0	0	+++	+++	Definite retinal arterio- sclerosis
115	Hypertension, arteriosclerosis, myocarditis	55	236/120	+	0	0	0	++	++	++	+++	+	0	++	0	Definite retinal arterio sclerosis, superficial hem- orrhages, copper wire arteries
116	Hypertension, arteriosclerosis	44	240/146	0	0	0	0	++	++	+++	+++	0	++	++	0	Definite retinal arterio sclerosis, superficial hem- orrhages, cotton wool spots, perivascular exu- dation
117	Hypertension, myocarditis, nephritis	50	242/150	+++	++	0	+++	+++	++	++	++	0	+	+++	0	Definite retinal arterio sclerosis, superficial and irregular hemorrhages, penciled fan, copper wire arteries
118	Hypertension, arteriosclerosis	54	242/126	+	0	0	0	0	++	++	++	0	0	+++	+++	Definite retinal arterio sclerosis
119	Hypertension	29	252/160	++	0	0	++	++	—	—	—	—	+	—	—	Yellow white spots, high degree of myopia, ves- sels could not be exam- ined
120	Hypertension, arteriosclerosis, chronic nephritis	57		+	+	0	0	+	++	+++	+++	0	0	+++	0	Definite retinal arterio- sclerosis, superficial hem- orrhages, buff spots

responsible for such differences in appearance as exist. The frosted window pane in the bedroom shows more delicately traced figures than that in the kitchen, where the humidity is higher and the heat greater and the frosting proceeds at a more rapid rate. The rate of formation may account for the difference in appearance of the macular fan or star.

The consensus of opinion is that the retinitis of chronic nephritis is due either to retinal arteriosclerosis alone or to retinal arteriosclerosis plus an added toxic, or rather an unknown toxic, factor. In addition to authorities already quoted, the former view is held by Schieck and Volhard,²¹ those inclined to the latter view are Benedict,²² Wagener,¹¹ Spir²³ and Ramsey²⁴.

Behan,²⁵ quoting Bulson,²⁶ disagrees with Benedict in that he believes that hypertension is the most prominent factor in the production of retinitis. He cites a case²⁷ of toxemia of pregnancy in which he saw the formation of macular star occur in two weeks. However, there is no statement to the effect that the patient had a normal blood pressure before the onset of the toxemia. Later in his article, he makes the rather remarkable admission that he finds 87 per cent of retinal vascular change and 100 per cent of retinal degeneration accompanied by hypertension. On the basis of Behan's figures, it is difficult to comprehend how he finds it possible to deny a relationship between vascular hypertension and retinal arteriosclerosis and retinitis. To sustain his position, he calls attention to the fact that about 20 per cent of the patients with retinal arteriosclerosis do not have hypertension. It is probable that if the previous vascular history of these patients were known, it would be disclosed that at some time they had a hypertension.

The question as to whether retinal arteriosclerosis precedes or is secondary to hypertension is still debatable. It is impossible to draw any conclusion from the cases included in this study. I have recently had

21 Schieck, F, and Volhard, F. *Netzhautveränderungen und Nierenleiden*, Zentralbl f d ges Ophth **5** 465, 1921, quoted by Benedict (footnote 22)

22 Benedict, W L. *Retinitis Associated with Disease of the Cardiovascular System*, New York M J **117** 741 (June 20) 1923. *Retinitis of Hypertension Plus Nephritis*, J A M A **78** 1688 (June 3) 1922.

23 Spir, E. *Retinitis in Chronic Nephritis*, Munchen Med Wchnschr **72**: 1030 (June 19) 1925, abstr J A M A **85** 556 (Aug 15) 1925.

24 Ramsey, A Maitland. *The Significance of Albuminuric Retinitis in Chronic Renal Cirrhosis*, Practitioner, **114** 354 (May) 1925.

25 Behan, J L. *The Fundus Changes in Nephritis*, J A M A **78** 1691 (June 3) 1922.

26 Bulson, A E, Jr. *Abstract of Discussion of Paper by George Slocum, A Study of Ophthalmoscopic Changes in Nephritis*, J A M A **67** 5 (July 1) 1916.

27 Behan, J L. *Proceedings Eye Section, New York State Med Soc*, April, 1922, quoted in footnote 25.

under observation two patients with the nephritic type of toxemia of pregnancy during their first pregnancy who had normal blood pressures during the first months, one of whom did not show any vascular change until she had had a markedly elevated blood pressure for from three to four months. The second patient had marked vascular changes six weeks after delivery of a seven months' fetus, at which time she had hypertension. In the first case, the fundi were examined frequently, but in the second case, only one observation was possible. As the patient did not give a history of nephritis, and as she had a normal blood pressure during the first months of her pregnancy, it may be assumed that the retinal arteriosclerosis manifested itself within a period of five months.

Benedict²² states that it is clearly evident that hypertension may be present long before changes in the retinal vessels take place. He says

In a great many persons having essential hypertension with a diastolic pressure of 160 or more and a systolic pressure of more than 200, the retinal vessels show not a single sign of thickening or other change.

As Benedict has access to a large clinical material which includes many ambulatory hypertensive patients, his opinion must be accorded considerable weight. However, the observations of O'Hare and Walker¹ and my observations in this series would indicate that while the number of these cases observed by Benedict may have been considerable on account of his large amount of material, the actual percentage in total cases studied may have been small. A small series of cases studied over a long period in which the date of onset of hypertension is definitely known will do much to answer this question.

GROUPS VI AND VII THE CHANGES IN THE EYEGROUND IN PATIENTS WITH CARDIAC DISEASE

The sixth group to be considered is the group of patients with chronic myocarditis or chronic myocardial degeneration, with or without hypertension, developing on a vascular basis, alone or combined with generalized arteriosclerosis, and patients with arrhythmia, angina pectoris and cardiac infarction. Chronic myocarditis was either the primary or the important secondary clinical diagnosis in this group.

To contrast with this group of patients with chronic myocardial disease is a group with chronic valvular disease. As far as could be determined, the cardiac disability in all of these cases developed on a rheumatic basis.

These groups comprise, respectively, fifty-six and fifteen cases, and the data are tabulated in table 9. In group VI, the fifty-six cases are arranged according to the level of the systolic blood pressure at the time of examination. This group is subdivided as follows (1) twenty-two

TABLE 9—Changes in the Eyeground in Cardiac Cases

Case No	Diagnosis	Age	Blood Pressure	Disks			Retinas			Arteries		Veins		Papill-Edema	Choked V. Cns	Remarks
				Increased Vascularity	Hemorrhage	Edema	Hemorrhage	Spots	Pigment	Tortuous	Irregular	Arteriosclerosis	Tortuous	Dilatation		
1	Cardiac infarction, chronic myocarditis	53	102/74	0	0	0	0	0	+	+	0	++	0	0	++	Doubtful retinal arterio sclerosis, few small buff spots
2	? Cardiac infarction, chronic myoe rditis	64	106/64	0	0	0	0	0	0	+	±	0	0	0	0	Definite retinal arterio sclerosis
3	Angina pectoris, chronic myocarditis	53	108/96	0	0	0	0	0	0	++	+++	+	0	0	0	Definite retinal arterio sclerosis
4	Cardiac infarction, chronic myocarditis	70	114/88	+	0	0	0	0	++	0	+	+	+	++	++	Definite retinal arterio sclerosis, beginning choroiditis
5	Chronic myocarditis, angina pectoris	56	114/74	0	0	0	0	0	0	0	0	0	0	0	0	None
6	Chronic myocarditis, angina pectoris	58	114/71	0	0	0	0	0	0	±	±	0	0	0	0	Doubtful retinal arterio sclerosis
7	Chronic myocarditis, arteriosclerosis	45	118/74	0	0	0	0	0	0	+++	±	+++	0	0	++	Definite retinal arterio sclerosis
8	Chronic myocarditis, arteriosclerosis	52	122/76	0	0	0	0	0	0	+	±	++	0	0	±	Doubtful retinal arterio sclerosis
9	Chronic myoe rditis, auricular fibrillation	70	122/74	0	0	0	0	0	0	0	++	++	0	0	++	Definite retinal arterio sclerosis, guttate choroiditis
10	Cardiac infarction, chronic myoe rditis	64	124/80	0	0	0	0	0	0	0	±	+	0	0	±	Doubtful retinal arterio sclerosis
11	Chronic myocarditis, arteriosclerosis	58	130/68	0	0	0	0	0	0	0	++	+++	0	0	++	Definite retinal arterio sclerosis
12	Chronic myocarditis, angina pectoris	44	136/76	0	0	0	0	0	0	0	±	±	0	0	0	Doubtful retinal arterio sclerosis
13	Chronic myocarditis, arteriosclerosis	57	136/76	±	0	0	0	0	0	0	+	0	0	0	+	Definite retinal arterio sclerosis
14	Chronic myocarditis, auricular flutter	65	136/94	0	0	0	0	0	0	0	±	++	0	0	+	Definite retinal arterio sclerosis
15	Chronic myocarditis, auricular fibrillation	52	138/86	0	0	0	0	0	0	++	++	+++	++	++	0	Definite retinal arterio sclerosis
16	Chronic myocarditis, auricular fibrillation	65	138/74	0	0	0	0	0	+	0	+	++	0	0	++	Definite retinal arterio sclerosis, buff spots
17	Chronic myoe rditis, chronic bronchitis	56	140/84	0	0	0	0	0	+++	0	+	+++	0	0	++	Definite retinal arterio sclerosis, choroiditis
18	Chronic myocarditis, auricular fibrillation	72	142/70	0	0	0	0	0	0	0	+	0	0	0	+	Definite retinal arterio sclerosis
19	Chronic myocarditis, arteriosclerosis	65	142/78	0	0	0	0	0	0	+	+++	++	0	0	++	Definite retinal arterio sclerosis
20	Chronic myoe rditis, arteriosclerosis	52	142/88	0	0	0	0	0	0	0	+	0	0	0	++	Definite retinal arterio sclerosis
21	Angina pectoris, chronic myocarditis	47	142/92	0	0	0	0	0	0	0	+	++	0	0	+	Definite retinal arterio sclerosis

TABLE 9—Changes in the Background in Cardiac Cases—Continued

Case No	Diagnosis	Age	Blood Pressure	Disks		Retinas				Arteries		Veins		Remarks				
				Increased Vascularity	Hemorrhage or Exudate	Edema	Hemorrhage	Spots	Pigment	Tortuous	Irregular outline	Arteriosclerosis	Tortuous		Dilatation	Papilledema	Choked Veins	
10	Chronic myocarditis, hypertension	60	182/98	±	+	0	0	0	0	0	+	+++	+++	+	++	+++	0	Definite retinal arterio sclerosis
11	Chronic myocarditis, fibrillation, arteriosclerosis, hypertension	63	184/92	0	0	0	0	0	+	0	+++	+	++	0	+	0	0	Doubtful retinal arterio sclerosis, superficial hemorrhages
12	Chronic myocarditis, auricular fibrillation, hypertension	62	184/100	0	0	0	0	0	0	+	+	+++	++	0	0	+++	0	Definite retinal arterio sclerosis
13	Chronic myocarditis, hypertension	53	186/98	0	0	0	0	0	0	0	+	+	++	0	0	±	0	Doubtful retinal arterio sclerosis
14	Chronic myocarditis, angina pectoris, hypertension	57	194/110	0	0	0	0	0	0	0	+	+++	++	0	+	++	++	Definite retinal arterio sclerosis
15	Chronic myocarditis, auricular fibrillation, hypertension	65	198/120	0	0	0	0	0	0	0	0	+++	+	0	0	+	0	Definite retinal arterio sclerosis, primary type retinal arteriosclerosis
16	Chronic myocarditis, arteriosclerosis, hypertension	52	200/110	0	0	0	0	0	+	0	+++	+++	+++	++	++	+++	++	Definite retinal arterio sclerosis, old superficial and small round hemorrhages
17	Angina pectoris, hypertension, arteriosclerosis	39	206/112	0	0	0	0	0	+	0	0	+++	+++	0	0	++	+	Definite retinal arterio sclerosis, copper wire arteries, small, round hemorrhages
48	Chronic myocarditis, arteriosclerosis, hypertension	57	206/132	+	+	0	0	0	0	+	++	+++	+++	0	0	+++	0	Definite retinal arterio sclerosis, in many small flame shaped, round and irregular hemorrhages, yellowish white spots
49	Chronic myocarditis, arteriosclerosis, hypertension	50	208/110	0	0	0	0	0	±	0	0	+++	++	0	0	++	0	Definite retinal arterio sclerosis, few small gray white spots
50	Chronic myocarditis, hypertension	72	218/122	0	0	0	0	0	0	0	++	0	++	0	0	++	0	Definite retinal arterio sclerosis
51	Chronic myocarditis, auricular fibrillation, hypertension	59	218/120	0	+	0	0	0	+	0	0	+++	+++	0	0	++	+++	Definite retinal arterio sclerosis, small round hemorrhages
52	Chronic myocarditis, hypertension	51	222/130	0	0	0	0	0	+++	0	+++	++	++	0	0	++	++	Definite retinal arterio sclerosis, small round hemorrhages and gray and white spots
53	Chronic myocarditis, hypertension	55	232/124	0	+	0	0	0	0	0	0	++	+	0	+	++	0	Definite retinal arterio sclerosis
54	Chronic myocarditis, auricular fibrillation, hypertension	71	238/126	0	+	0	0	0	+	0	++	+++	+++	0	+	+++	0	Definite retinal arterio sclerosis, small flame shaped hemorrhages
55	Chronic myocarditis, arteriosclerosis, hypertension	50	242/120	+	+	+	+	+	+	+++	++	++	++	++	0	+	+++	Definite retinal arterio sclerosis, choroiditis, secondary optic atrophy, small white spots
56	Chronic myocarditis, hypertension	71	275/118	0	0	0	0	0	+	0	++	+	++	0	+	+++	0	Definite retinal arterio sclerosis, small round hemorrhages

57	Chronic valvular disease, mitral stenosis	18	82/40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
58	Chronic valvular disease, aortic and mitral stenosis and insufficiency	13	102/0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis, pulsation in arteries and veins
59	Chronic valvular disease, mitral stenosis auricular fibrillation	29	106/60	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0	No retinal arteriosclerosis
60	Chronic valvular disease, aortic stenosis and insufficiency	49	112/90	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
61	Chronic valvular disease, mitral stenosis	29	112/?	0	0	0	0	0	0	0	0	0	±	0	0	0	0	0	Doubtful retinal arterio sclerosis
62	Chronic valvular disease, mitral stenosis and insufficiency	23	114/66	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	No retinal arteriosclerosis
63	Chronic valvular disease, aortic insufficiency, mitral stenosis and insufficiency	15	118/0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis, pulsation in arteries and veins
64	Chronic valvular disease, mitral stenosis	15	122/60	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
65	Chronic valvular disease, mitral stenosis and insufficiency	37	128/80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	++	No retinal arteriosclerosis
66	Chronic valvular disease, mitral stenosis	32	134/60	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
67	Chronic valvular disease, mitral stenosis	45	148/98	0	0	0	0	0	0	0	0	++	++	++	0	0	±	0	Definite retinal arterio sclerosis
68	Chronic valvular disease, auricular fibrillation	15	148/90	0	0	0	0	0	0	0	0	++	++	++	0	0	+	0	Definite retinal arterio sclerosis
69	Chronic valvular disease, mitral stenosis and insufficiency	46	150/84	•	0	0	0	0	0	0	0	0	++	0	0	0	+	++	Definite retinal arterio sclerosis
70	Chronic valvular disease, mitral stenosis insufficiency, aortic insufficiency	19	150/0	0	0	0	0	0	0	0	0	++	0	++	0	0	0	+++	Doubtful retinal arterio-sclerosis, arteries and veins, pulsate, choroiditis
71	Chronic valvular disease, aortic insufficiency and stenosis	50	152/78	0	0	0	0	0	0	0	0	0	+	0	0	0	+	0	Definite retinal arterio-sclerosis

patients without hypertension and with a systolic blood pressure of 145 mm or below and (2) thirty-four patients with hypertension and with a systolic blood pressure above 145 mm. A comparison of the incidence of retinal arteriosclerosis is made in table 10.

SUMMARY OF GROUP VI

An examination of the data reveals that irregularity of lumen and arteriovenous compression are not always present in the same degree. In fourteen cases in which there was marked arteriovenous compression, ten patients showed definite irregularity of the lumen of the arteries, while in four cases it was only slight or doubtful. In twelve of the foregoing cases, definite changes occurred in the arterial reflex which indicated thickening of the arterial wall, while in contrast definite irregularity of the lumen was observed in seven cases, with slight or no arteriovenous compression. Case 35 is the outstanding example. My impression is that these variations are due largely to the degree of

TABLE 10—*Retinal Arteriosclerosis in Group VI*

	Definite, Percentage	Doubtful, Percentage	None, Percentage
Without hypertension	68.2	27.3	4.5
With hypertension	91.2	8.8	0.0

intimal change and to the thickening of the media which are present in the individual case, and particularly to the change that predominates.

The most marked pressure effects are usually seen in the cases in which there are thick copper wire arteries, in these cases, the arteries and veins usually cross at right angles. As a result, the compression is clear-cut, and the venous channel is obliterated on each side of the vessel for a distance approximately equal to the central blood column. This, no doubt, corresponds to the thickness of the arterial wall, which is not visible. When by chance the vein crosses the artery, "mounding" of the vein is produced, and the vein forms an inverted loop corresponding to the size of the artery.

Some degree of dilatation of the veins occurred in five of fifty-six cases, and in only one instance in the absence of definite arterial sclerosis. In one case (29), phlebosclerosis was seen. The changes in the veins, with the exception of the compression effects, seem to hold a position of only secondary importance in the recognition of retinal arteriosclerosis.

Some degree of choroid vessel sclerosis was visible with the ophthalmoscope in eighteen of twenty-six cases, and in all but two instances it was associated with definite retinal arteriosclerosis. On the other hand, it was absent in thirty cases in which there was definite retinal arterio-

sclerosis In this series, it was not as frequent as the studies of Cohen²⁸ would indicate It is his opinion that the basic pathologic change in the eyeground is a primary choroidal arteriosclerosis He considers that the edema of the disks, hemorrhages and spots result wholly from this factor or in combination with some unknown factor He also states that in many cases sclerosis of the choroidal vessels is more marked than retinal sclerosis, or may be marked when retinal arteriosclerosis is absent

It would seem, then, from my series, that sclerosis of the choroidal vessels, recognizable with the ophthalmoscope, is rarely observed before retinal arteriosclerosis It must be taken into account, however, that Cohen's statements are in part based on a study of actual pathologic specimens Sclerosis of the choroidal vessels in this respect frequently seems to be associated with changes in the disk and the presence of hemorrhages, spots and pigment Some of these changes were present in thirteen of the eighteen cases of sclerosis of the choroidal vessels and in only thirteen of thirty-eight cases in which such sclerosis was not present However, in the diabetic group it was a rather frequent occurrence and disk changes were rare No conclusion can therefore be drawn from my observations

The changes in the disk and in the retina are not worthy of extended comment From the table, it may be observed that the incidence is greater in the patients with the higher pressures

If the group as a whole is considered, the observations suggest that in the majority of cases the myocardial degeneration has probably developed on a basis of previous hypertension (if the assumption that retinal arteriosclerosis is produced by hypertension is correct), and that the patient who has a normal blood pressure at the time of examination has lost his hypertension either prior to, or with the development of, the myocardial insufficiency, and that the degeneration may have been initiated because of general sclerosis of the precapillary vessels, if it is accepted that the condition of the retinal vessels reflects the condition of the small vessels throughout the body This opinion was first expressed by Gunn,²⁹ and it has since been reiterated by numerous observers These observations conform with the clinical observations of Fahr,³⁰ who is of the opinion that 75 per cent of chronic myocarditis originates on the basis of hypertension

28 Cohen, M. Significance of Pathological Changes in the Fundus, *J A M A* **78** 1694 (June 3) 1922

29 Gunn, Marcus. *Tr Ophth Soc, London* **18** 356, 1898, quoted by Moore (footnote 2)

30 Fahr, G E. Hypertension Heart, Most Common Form of So-Called Chronic Myocarditis, *J A M A* **80** 981 (April 7) 1923

The idea of searching for evidence of previous hypertension in the eyegrounds of patients who have chronic myocarditis and whose blood pressure is low or normal was suggested to me by O'Hare. He called to my attention the possible connection between generalized sclerosis of the small vessels and chronic myocarditis. The retinal and clinical aspects of patients with chronic myocarditis will be considered more fully in a future publication.

In one patient under my observation who had definite retinal arteriosclerosis with a blood pressure of 136 systolic and 94 diastolic after rest in bed and digitalis therapy, the blood pressure rose in twenty-four days to 240 systolic and 140 diastolic. Fahr observed a considerable rise in blood pressure in the majority of patients whose condition was diagnosed as myocardial failure while they were in the hospital under treatment.

In comparing the group of patients with chronic valvular disease (table 7) with that in which the patients suffered from chronic myocarditis, an absence of retinal sclerosis is found in ten of fifteen cases. One case shows doubtful, and four cases definite, retinal arteriosclerosis, however, the latter patients had systolic blood pressures over 145 mm and had reached an age when degenerative changes in the vascular system might become manifest. Changes in the disk and in the retina were absent. Three of four patients with aortic insufficiency showed pulsation both in the arteries and in the veins. Two patients of twelve in this series whose condition was diagnosed as mitral stenosis showed slight hypertension and mitral stenosis. Boas and Fineberg³¹ found 29 per cent hypertension in 135 cases of mitral stenosis. Only five of their patients 40 years of age or under had hypertension. The patients in my small series have an average age well below 40, which doubtless accounts for the low incidence of hypertension and retinal arteriosclerosis in mitral stenosis.

SUMMARY

1 A study of twenty cases of thyroid disease with increased basal metabolism shows a rather striking absence of retinal arteriosclerosis when patients in the sixth decade are eliminated.

2 In forty-seven diabetic patients of all ages (excluding children under 12 years) with and without hypertension, the incidence of definite retinal arteriosclerosis was 36.1 per cent in the latter and 81.8 per cent in the former. In both groups considered together, it was 42.5 per cent. These observations indicate that hypertension may play an important rôle in diabetes. The average age of diabetic patients with definite retinal arteriosclerosis was 57.7 years, while in patients showing doubt-

31 Boas, Ernst P., and Meyer H. Fineberg. Hypertension in Its Relationship to Mitral Stenosis and Aortic Insufficiency, *Am J M Sc* **172** 648 (Nov.) 1926.

ful or no retinal arteriosclerosis, the average age was 33 years. No patient under 30 years of age showed either definite or doubtful arteriosclerosis. If the presence of retinal arteriosclerosis is an index of sclerosis of the small vessels in other parts of the body (pancreas included), sclerosis of the small vessel may be an important factor in the production of diabetes after 50 years of age.

Likewise, it does not appear to be a factor in the production of diabetes in the young person. Sclerosis of the choroidal vessels is more frequent in diabetes than in the other conditions studied, changes in the disk are infrequent. If the ophthalmologist or internist sees eyegrounds exhibiting abnormally red retinas, numerous small round hemorrhages, groups of small yellowish-white and grayish-white spots on the central field of the retina, arteries with sclerotic changes, an well defined sclerosis of the choroidal vessel in the periphery of the retinal field with normal or nearly normal disks, in a person past middle life, he should strongly suspect diabetes.

3 In a small series of cases of acute and subacute nephritis, retinitis was conspicuous by its absence. The two patients with retinitis both had hypertension.

4 Retinitis occurs with greater frequency in chronic nephritis than in vascular hypertension. Renal retinitis presents certain changes, such as marked papilledema, retinal edema, cotton wool spots and coarse fan and star formation that suggest renal involvement. In retinitis caused by hypertension, these changes are less frequent, but all may occur. Retinitis resulting from hypertension may therefore be indistinguishable from renal retinitis. The change in the eyeground in both instances result from vascular change and diminished blood supply to the retina. It is suggested that such difference in appearance as exists is probably due to the rate at which the degenerative changes occur.

5 A study of the changes in the eyegrounds in fifty-six patients with and without hypertension, in which chronic myocarditis was either the primary or the important secondary diagnosis, revealed the presence of definite retinal arteriosclerosis in 91.2 per cent of the former and in 68.2 per cent of the latter. This observation (if certain criteria previously set forth in this article may be accepted) indicates that previous hypertension may play an important part in the etiology of chronic myocarditis, with and without hypertension.

6 In chronic valvular disease that had developed on a rheumatic basis, retinal arteriosclerosis was absent in two thirds of the cases, and when definite retinal arteriosclerosis was present, it occurred in association with elevation of the blood pressure and in patients who had reached an age when degenerative changes in the vascular system might become manifest.

ATYPICAL SPRUE

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The diagnosis of sprue is as yet on an unsatisfactory basis. In the late or advanced stages of the disease, clinical recognition is comparatively easy. In its earlier and initial course, it is recognized with considerable difficulty and uncertainty, and diagnosis really rests on its later development into a more or less classic picture. So far as evidence is available, we do not find a close correspondence between the symptoms and the gross pathologic condition. This observation leads to the inference that disturbance of function precedes the establishment of objective cellular changes by a variable and indefinite time. In this respect sprue resembles subacute myelinic degeneration of the spinal cord.

A diagnosis based on the characteristic diarrhea, stomatitis and afebrile course does not include many early cases which later prove to be sprue. Moreover, after this classic picture has been present even for years, one or all of these features may be absent, and the condition may appear as an essential anemia or combined sclerosis. The difficulties are enhanced by ignorance of clearly defined etiology and by an absence of pathognomonic tests. The term "sprue" has loosely covered a rather large and indefinite group of clinical conditions, including the classic picture and cases that grade off in several directions and present only a smattering of one or more of the prominent features of the genuine disease. In the first place, there are the mild but persistent diarrheas, some of which later develop into classic sprue, but in many of which the patients recover without such progression. Physicians see the more characteristic cases which follow or are initiated by dysentery or acute enterocolitis, the cases in which gastric disturbances are the prominent feature, and diarrhea is absent, cases with a history of diarrhea in which the stomatitis and diarrhea have disappeared, but in which the stools are bulky, and the asthenia and loss of weight are progressive, and a group of borderline cases in which the features of sprue are definite, but in which intercurrent clinical and pathologic features are also prominent. Some of these borderline cases are similar to the classic pernicious anemia of Addison's description, and the anemia itself is identical with

the latter Reference has been made to these mixed or borderline cases in a former article¹

The following case reports are further illustrations of this borderline group Some present evidence of triple system involvement and may be classified as atypical sprue, or perhaps better under a new heading that will indicate the more complex clinicopathologic picture of sprue, pernicious anemia and combined nerve degeneration

In regard to etiology the presence of Ashford's *monilia* has been inconstant in these cases, and we are not prepared to accept its pathogenicity as established for sprue itself and even less for these atypical cases The idea of a gastro-intestinal toxin of a group type, not limited to a single chemical entity, seems now the most logical working hypothesis The work of Minot,² relating to high protein and nuclear diets in pernicious anemia, has been confirmed in our experience, and we have reviewed the dietary treatment of sprue from this standpoint The suggestion arises naturally that the factor of deficiency in vitamin or protein may have an etiologic bearing on sprue, pernicious anemia and combined degeneration A later report will be devoted to our own experience along these lines

CASE REPORTS

CASE 1—*History*—J F A, a private patient,³ a man, aged 47, an American, had spent several years in Japan and in travels about the Orient, including China and the Philippines The previous history included only typhoid and influenza In Japan, in 1923, he suffered a sudden hard chill, followed by high fever and diarrhea He did not have dysentery, but he had much colic Recovery seemed complete in four days One month later the stools began to be typical of sprue, and stomatitis soon followed Four months later, when he arrived in San Francisco, examination showed extreme emaciation and a tawny yellow skin The abdomen was swollen, tympanitic and tender, the liver and spleen were not felt The Wassermann reaction was negative, and the urine was normal The stools were negative for blood, parasites and yeasts The coagulation time of the blood was normal Examination of the blood showed red cells, 1,850,000, white cells, 4,100, hemoglobin (Sahli), 36 per cent, polymorphonuclear cells, 48, and lymphocytes, 47 There was great variation in the size and shape of the red cells, the color index was 1

The blood counts remained similar to this for several months, then gradually returned to normal Five months after the man arrived in this country, his health was apparently normal, and against advice he returned to Japan After three months in Japan, his blood count was still normal, and he did not have any symptoms He then returned to San Francisco in July, 1924 Two days after he landed, stomatitis and stools typical of sprue suddenly developed Diarrhea, weakness and occasional mild stomatitis were present to some degree during the next two months

1 Reed, Alfred C, and Wyckoff, Harry A Common Picture of Sprue, Pernicious Anemia and Combined Degeneration, Am J Trop Med 6 3 (May) 1926

2 Minot, G R Treatment of Pernicious Anemia by Special Diet, J A M A 87 7 (Aug 14) 1926

3 The earlier part of this history has been reported (footnote 1)

After two and a half months in this country, he again, against advice, returned to Japan, he still had some gastro-intestinal disturbance, weakness and a recurrent anemia with a high color index. Three weeks after reaching Japan, he was attacked by intense epidemic intestinal influenza with fever. This gradually led to a recurrence of typical and severe sprue. He began to lose weight. The blood rapidly degenerated to the following picture: red cells, 2,108,000, white cells, 4,600, polymorphonuclear cells, 58 per cent, lymphocytes, 31, mononuclears, 9, hemoglobin (method not given), 47 per cent, color index, 1.12. Numerous nucleated red cells, macrocytes and abnormal shapes were found.

He stayed in Japan for five months. When he reached San Francisco again on April 7, 1925, examinations showed extreme emaciation, yellow, waxy pallor and extreme weakness. He suffered from a constant watery diarrhea. The stools were free from blood, parasites and yeasts. The blood count on April 8 was as follows: red cells, 1,400,000, white cells, 2,325, polymorphonuclear cells, 54 per cent, lymphocytes, 41, eosinophils, 5, hemoglobin (Sahli), 33.2 per cent, and color index, 1.18. Megaloblasts, polychromasia, abnormal shapes and sizes were numerous.

Improvement followed a series of transfusions, until his clinical condition became practically normal in July, 1925, although the blood was still anemic, but the color index was normal. In September, the anemia again advanced and was accompanied by a marked increase of numbness of the hands and feet and by an extreme clumsiness in the motor functions, especially of the hands and feet. Neurologic examination by Dr. Joseph Catton gave the following objective observations: "Definite disturbance in sensation over corresponding areas on outer surface of each foot. In view of the usual findings in cases presenting the blood picture seen in this case, I would be inclined to place the trouble in the cord." There was a steady progression in the anemia, wasting and diarrhea, accompanied by periods of stomatitis. No further symptoms appeared referable to the spinal cord. Transfusions gave only temporary relief. In February, 1926, the clinical picture was that of pernicious anemia, with lemon-hued skin and a typical blood picture of a rather aplastic type.

On March 12, 1926, the blood reached its lowest count, and the patient was in a dying condition, with severe air hunger and cramps in the legs and chest. The blood count was remarkable, as follows: red cells, 835,000, white cells, 5,200, polymorphonuclear cells, 75 per cent, lymphocytes, 23, mononuclears, 2, and hemoglobin (Sahli), 12 per cent. Red cells showed numerous macrocytes and microcytes, the former predominating. Numerous abnormal shapes, some stippling of red cells, occasional normoblasts and a few megaloblasts were present. The actual hemoglobin reading was too low to be entirely accurate.

A new series of transfusions gave temporary respite and comparative comfort for about three months, during which time they alone kept him alive. A total of nineteen transfusions were given during the entire illness. Death occurred on July 3, 1926, in Letterman Hospital, to which the patient was admitted on June 9. During the last month of life, the blood count was maintained fairly well and showed a remarkable "come-back" from the extremely low picture of March 12. On the day before death, the count was as follows: red cells, 2,080,000, white cells, 6,000, hemoglobin (Dare), 55 per cent, polymorphonuclear cells, 62 per cent, lymphocytes, 35, eosinophils, 2, and transitionals, 1. The urine was constantly normal. The results of fractional gastric analysis two weeks before death are shown in table 1.

The degrees of acidity given in table 1 and elsewhere in this article, when not otherwise indicated, are computed on the basis of the amount of tenth normal sodium hydroxide required to neutralize the acid in 100 cc. of filtered gastric contents.

Postmortem Examination—General examination showed extreme emaciation. The height was 5 feet, 9 inches (175.2 cm), and the weight was about 110 pounds (49.9 Kg). The surfaces of the abdomen, arms and legs were covered with

small petechial hemorrhages There was practically no postmortem lividity There was no subcutaneous fat, and the musculature was extremely pale, thin and small The peritoneum was smooth and moist The appearance of the chest was not remarkable except for a terminal bronchopneumonia The spleen was small and flabby and weighed 150 Gm, the cut surface was dark red and studded with numerous small white plaques The liver weighed 1,125 Gm and had a dark red and wet cut surface, the capsule was smooth and glistening Grossly, the gall-bladder was normal The appearance of the pancreas was not remarkable

The entire gastro-intestinal tract was dull gray, the mucosa of the sigmoid seemed thickened, while the wall of the small intestine was thin, and the mucosa was almost entirely atrophic The lower portion of the small intestine was entirely smooth, while the upper portion showed normal folding of the mucosa The stomach was small and apparently free from pathologic changes

The suprarenals were small, but seemed normal The renal pelves were dilated The glandular and osseous systems were not remarkable

Sections of the cervicodorsal cord examined by Dr William Ophuls were normal in appearance

Pathologic Diagnosis—The diagnosis was sprue, bronchopneumonia, anthracosis, reticulo-endothelial hyperplasia of the liver with hemosiderin pigmentation, atrophy and degeneration of the muscle of the heart, hydronephrosis

Comment—This case was primarily typical of sprue, with the ordinary early secondary anemia and terminated in the triple system syndrome, which involved

TABLE 1—Results of Fractional Gastric Analysis

Free hydrochloric acid	18	15	26	22	25
Total acid	30	24	50	42	44

the gastro-intestinal tract, the blood and the nervous system As the sprue developed, and there was a relapse and recurrence, pernicious features developed in the blood until the picture was that of true pernicious anemia, gradually changing into an aplastic type There were definite and consistent nervous symptoms In the light of the knowledge of the relation of symptoms to pathologic conditions in subacute degeneration of the spinal cord, this case presents indications of damage to the cord which cannot be ignored Negative results of postmortem examination of the cord do not change the fact that the cord functioned abnormally in life A neurologic study of the relation of pathologic conditions to symptoms and of the occurrence of subacute myelomic degeneration in the peripheral nervous system will be published shortly by Joseph Catton, including a neurologic review of several of the cases reported here

CASE 2—History—S W, a man, an American, aged 58, was first seen on July 1, 1926 He had had a severe attack of malaria in 1900, but none since that date and otherwise no noteworthy illnesses had preceded the present one He was born in England, and went to the eastern part of the United States at the age of 10, in 1898, he went to the Philippines, where he has resided since His average weight was 130 pounds (59 Kg), but for the last few years it has been 125 pounds (56.7 Kg)

The present illness began about three years before presentation with an attack of what was probably bacillary dysentery, for which he was treated and cured by specific serum From that time he had had constant indigestion, with excessive flatulence, fermentation and occasional looseness of the bowels, but he did not have pain, nausea or vomiting at any time At times his mouth would become dry, irritated and slightly sore, frequently sour foods would cause pain in the mouth Starches and sweets aggravated the indigestion He could eat large quantities of strawberries with ease and improvement One year before presenta-

tion he had an attack of sore mouth and tongue of moderate severity. He did not use tobacco or alcohol. Anorexia was marked. This status persisted to the time when this article was written with a gradual loss of weight to about 115 pounds (52.1 Kg) and a gradual decline in strength and energy. He felt that he had become somewhat irascible and irritable. This change in disposition is a rather common feature in ordinary sprue.

Examination—Examination in July, 1926, showed a slight, rather pale man. Results of a neurologic examination were negative. The mouth was normal, in fact, with the exception of a slightly tympanitic abdomen, he was entirely normal.

Laboratory Observations gastro-intestinal roentgenograms showed a normal colon. There was an inconclusive suggestion of duodenal ulcer, but it was disproved by further study. The chest was normal, except for scarring of the hilum and the pleura. The Wassermann reaction was negative. The blood calcium was 9.97 mg. Examinations of stools were repeatedly negative for *Protozoa* or other parasites and *Monilia*, except for a few ova of *Trichuris*. A stool examined bacteriologically by Dr. E. C. Dickson showed a predominant gram-negative picture without streptococci or yeasts. Cultures were negative for pathogens. The stools showed an excess of fat. The urine was normal except for the presence of urobilin.

The gastric contents during fasting did not show free acid, the total acid was 10. The first specimen was too small to examine. The second specimen showed a free acid of 15 and a total acid of 35, and the third specimen showed a free acid of 20 and a total acid of 45. The blood count was as follows: red cells, 2,870,000, white cells, 5,150, polymorphonuclears, 63 per cent, lymphocytes, 33, eosinophils, 1, basophils, 2, transitional, 1, reticulated red cells, 1 per cent of the total red cells, hemoglobin (Sahli), 67 per cent, color index, 1.15. No nucleated red cells were seen. Many large, rather faintly staining red cells and moderate poikilocytosis were present.

Treatment and Course—For two months the only treatment consisted of high purine diet, and the blood count was as follows on October 6: red cells, 2,800,000, white cells, 7,800, hemoglobin (Dare), 62 per cent, color index, 1.1. Antisicytosis was present. The platelets were normal, and there was no stippling.

The diet was then changed to one typical for patients with sprue, containing an abundance of fresh fruits, berries, rare meat and fresh milk, while a restriction was placed on starches and sugar. There was immediate improvement in the digestive condition, the symptoms entirely disappeared, and the appetite returned. During October, a series of four transfusions was given, with iron cacodylate daily by vein. The blood count improved until, on Nov. 23, 1926, it was as follows: red cells, 4,080,000 and hemoglobin (Dare), 82 per cent, the color index was 1.02.

Clinically, the patient is well. His prognosis is probably bad if he returns to the Philippines and good if he remains in this country.

Comment—This case illustrates the "dysentery" onset of a case of sprue atypical in the absence of characteristic stools, with anemia which had the pernicious features of high color index and increased size of red cells, but which did not yield to a high protein and nuclear diet and which showed almost a specific reaction to a diet for sprue and blood transfusions. The patient did not show subjective or objective evidence of nerve degeneration at any time. It is to be noted that his blood calcium was at a high normal figure, and the contents of the stomach showed a rather low acidity. This is a comparatively early case which may possibly develop into pernicious anemia or in which the typical symptoms of sprue would probably appear if the patient should live in a climate in which the disease was endemic.

CASE 3—History—(Private) S. I., a white male, aged 50, had lived in Pennsylvania all of his life until he came to southern California in 1920, except for three months spent in Georgia in 1918. As a child he had had whooping cough, measles and frequent colds and tonsillitis, attacks of tonsillitis did not

disappear until tonsillectomy was performed in 1924. He had not had any other acute diseases. On two occasions he had had mild dysenteric attacks, apparently caused by the consumption of bad food during hot summer weather, otherwise, his gastro-intestinal condition was excellent until this illness. As a young man, he was told that he had a mitral leak, but it never produced symptoms. His average weight in mature life had been 144 pounds (65.2 Kg). He led an active, normal life, he did not indulge in excesses and did not have any complaints.

His present illness began in December, 1920, when, his general health being normal, he noticed that his mouth was so sore that he could not smoke. This condition was followed by anorexia, indifference to food and indigestion associated with extreme flatulence. The bowel movements were regular, but bulky, pultaceous or mushy. He had increasing asthenia and sleepiness and tired easily. In the following spring, these symptoms became more severe, and paresthesias were noted, especially at the roots of the toes. Each spring for five years, that is, with the onset of hot weather, since coming to California, he had had a recurrence of spruelike symptoms. These attacks had increased in intensity and were accompanied by a gradually increasing anemia, which tended to take on certain pernicious features. In February, 1924, the paresthesias extended to the ulnar distribution of the left hand. During the succeeding summer, he was much run down, lost energy and ambition, was easily exhausted and could not stand exercise. In October, 1924, the paresthesias became much worse. A tonsillectomy was performed. The blood count at that time showed 2,700,000 red cells, 68 per cent hemoglobin and a low white count.

From that time, he gradually lost ground, and the nervous symptoms increased. Gastro-intestinal roentgenograms in October, 1924, showed only quick emptying of the stomach and a spastic colon. There was achylia, with low combined acid in the stomach. Flatulence and fermentation increased. He had several lesions of the skin which were pronounced eczema. A series of injections of iron cacodylate were not beneficial. Intermittent claudication appeared in both legs. Transfusion was performed three times, and the blood count rose to 4,000,000. In January, 1925, it was said that *Giardia* was found, an observation which was not confirmed by us. Thymol was given and resulted in an acute enteritis with fever and severe pain in the right lower quadrant. In the following month he improved, his weight increasing to 148 pounds (67.1 Kg), and he felt better than he had in several years. This improvement lasted until warm summer weather, when the former symptoms again recurred, and he lost 16 pounds (7.3 Kg). Exhaustion, stomatitis and flatulence were excessive. Some improvement followed another transfusion in November, 1925.

Examination—He came under the observation of one of us on Jan. 20, 1926. Physical examination showed a rather poorly developed, asthenic looking man about 50 years of age. The skin was distinctly sallow, but not yellow. The color of the mucous membranes was fairly good. The appearance was definitely not that of pernicious anemia. There was some retraction of the gums and a mild stomatitis. The heart was somewhat enlarged to the left and had a soft systolic apical murmur, also heard at the base. The spleen was easily palpable, the liver not enlarged. The abdomen was tympanitic. Dr. Alderson reported that the patient had a generalized seborrheic dermatitis which he considered secondary to the intestinal condition.

Laboratory tests showed the following blood count: red cells, 2,600,000, white cells, 4,725, polymorphonuclears, 45 per cent, lymphocytes, 36, hemoglobin (Sahli), 60 per cent, mononuclear and transitional cells, 10 per cent, eosinophils, 7, basophils, 2, color index, 1.15.

There were no nucleated cells. Moderate poikilocytosis, an occasional macrocyte with diffuse bluing and many small red cells were present. The polymorphonuclear white cells had an increased amount of lobulation, some showing seven lobes.

The Wassermann reaction was negative. The blood calcium was 8.65 mg per hundred cubic centimeters. On the following day the blood calcium was 9.812 mg, and the blood count showed red cells, 2,227,000, white cells, 4,200, polymorphonuclears, 48 per cent, lymphocytes, 43, eosinophils, 7, basophils, 1, transitionals, 1, hemoglobin (Sahli), 66 per cent, and a color index of 1.5.

No parasites were found on repeated, adequate examinations of the stools. Specimens contained bile pigment and increased amount of fat, but no blood. Smears showed no cells, but Dr. E. C. Dickson found many bacteria, including long chains of streptococci, many gram-positive cocci and many gram-positive bacilli. Cultures showed a mixed growth of hemolytic and nonhemolytic streptococci, *Staphylococcus albus* and a mucinous-appearing gram-negative bacillus. No growth was obtained of dysentery bacilli, *B. welchii* or *oidia*. Inoculations of rabbits were also negative for these organisms.

The urine was constantly normal. The temperature while the patient was under observation ranged between 97.4 F and 99.4 F. The pulse and respiration rates were normal.

Studies of the gastro-intestinal tract by roentgenograms with those taken after a barium enema, were made by Dr. R. R. Newell, and did not show any abnormality.

Examination of the contents of the stomach gave the results shown in table 2.

TABLE 2—*Acidity as Shown by Contents of Stomach*

	Free HCL	Total acidity
Fasting	0	10
Specimen I	0	5
Specimen II	0	5
Specimen III	0	10
Specimen IV	0	Not sufficient quantity

There was no lactic acid or occult blood, but much mucus.

Dr. Joseph Catton summarized the neurologic examination as follows: A physiologic functional change was present, which was capable of more or less complete restoration to normal if the non-neurologic phases of the case were improved or cured. The physiologic function of the spinal cord had been disturbed by toxins, but its structure was intact. Definite subacute degeneration of the posterolateral tracts of the spinal cord had taken place. There had been paresthesias of all four extremities, commencing with the fingers and toes and later involving the legs. On one occasion while playing cards on a train his left arm rested on a window ledge in such a manner that there may have been some exposure to draft and trauma. Following this, there were extensive paresthesias in the left ulnar distribution, which were similar to paresthesias that occurred later in his illness without trauma or exposure. There were no symptoms referable to the cranial nerves. The only motor symptom, in addition to generalized weakness, was an increase in the muscle tone of the lower extremities following extensive exercise. The organic reflexes and the autonomic nervous system were undisturbed. Abnormal psychotic elements were not present. The cranial nerves were normal. The finger-tips showed a diminution of touch, pain and temperature sensations. These sensations were also delayed and were accompanied by paresthesias. The same phenomena were found on the tips and plantar surfaces of the great toes. There was a small spot over the inner side of the left ankle in which touch, pain, temperature and vibratory senses were impaired. Stereognosis was normal. There was a slight disturbance in balance when the patient stood on one foot with eyes closed. The upper tendon reflexes were within normal and were a little greater on the left side. Patellar reflexes were increased, with no ankle clonus. There were no pathologic signs in the great toe.

Dr H Y McNaught, who examined the nose and throat, reported a low grade ethmoid infection of secondary importance which was to be attacked directly only if there was no other line of effective treatment

Duodenal drainage by the Lyons-Meltzer method for the bile system did not show any cells, but many bacteria, including long chains of streptococci, many gram-positive cocci in pairs, singly and in clusters and many gram-positive bacilli. Cultures showed a mixed growth of hemolytic and nonhemolytic streptococci, *Staphylococcus albus* and a mucinous-appearing gram-positive bacillus seen also in stools. These studies were made by Dr E C Dickson, who felt that in spite of the low acidity of the stomach, the streptococcal content of the bile was above normal. It is to be noted that the finding of *Giardia* was reported in an earlier examination elsewhere, but this organism was not found by us

Progress of Case—In spite of a rather unfavorable regimen of work, the patient's energy and weight had improved on March 12, 1926, and there had been only a few episodes of fermentative, loose stools. The sensory disturbances, which were subject to a wide diurnal variation, had abated considerably. The first to appear, the greatest in intensity and the last to recede were in the distal portions of the extremities. Undoubtedly a large share of this damage was peripheral

On April 14, 1926, the blood count was red cells, 3,670,000, white cells, 6,200, polymorphonuclears, 64 per cent, lymphocytes, 36, hemoglobin, 75 per cent, color index, 1.04, poikilocytes, a few, macrocytes, very few, microcytes, a few. The patient's weight had increased 10 pounds (4.5 Kg), and strength, energy and endurance were much improved. He had been on a classic diet for patients with sprue which had a high purine content. Hydrochloric acid was given in large doses with meals and pancreatic extract with bile salts. Occasional courses of castor oil were used, and for the fermentation periods, a mixture of tannalbin, kaolin and thymol

CASE 4—History—A J M, a white man, aged, 59, with a clinical diagnosis of transverse myelitis, had lived in the Philippines from 1904 to 1917, during which time he had suffered a mild attack of dysentery of undetermined type. He had typhoid at 21 years of age

The history of his illness was evidently incomplete. He was under observation only one week, and while he was said to have been in good health until January, 1926, the pathologic condition at death was scarcely compatible with so short an illness. His illness was said to date from an attack of influenza in January, 1926, when he developed diarrhea which persisted to the end. The stools were foamy, foul and copious, from four to eight a day. He failed rapidly and lost from 40 to 50 pounds (18.1 to 22.7 Kg) in weight. There was no history of nausea, vomiting or abdominal pain, but he had a sore mouth for the last three months of his life, and a constant mild indigestion. He was bedfast for the last three weeks

Examination—Physical examination revealed that he was physically helpless and emaciated, with a mild icteric tinge. There was marked pyorrhea, gingivitis, sordes and a number of carious teeth. The liver was palpable on deep inspiration and slightly tender. The spleen was not palpable. Neurologic examination revealed "marked combined sclerosis." The blood count was as follows on June 18: red cells, 2,500,000, white cells, 6,800, hemoglobin, 50 per cent

On June 21, a transfusion of 500 cc of blood was given. On that day the platelets were 83,600, and with hypotonic sodium chloride solutions hemolysis began in 0.32 per cent and was complete in 0.26 per cent

The contents of the stomach showed absence of free hydrochloric acid during fasting and in the two fractional specimens examined. The total acidity was 12, 6 and 4, respectively

The urine was normal. Examinations were not made of the stools or spinal fluid. A Wassermann test was not made. The patient died on June 23

Autopsy—Autopsy showed an advanced degeneration of the lateral and posterior columns of the spinal cord, chronic cerebral leptomeningitis, pulmonary edema and

some hemosiderin in the liver cells. No pathologic condition was noted in the gastro-intestinal tract except that the small intestine contained mucus, and the colon was distended with foul-smelling, slate-colored material.

CASE 5—History—G B, aged 55, colored, who had lived in the Philippines for eighteen years, had been in a hospital in 1901 with "sour stomach" and diarrhea. In 1903, he had been operated on for ventral hernia. The definite history of his illness dated from June, 1923, when he had a painless diarrhea with sore mouth, which persisted. In 1924 he had entered a hospital in the Philippines with "marked anemia." The record of the blood picture in that illness was not available. A roentgenogram at that time demonstrated a constriction in the descending colon and intra-abdominal adhesions. Improvement was temporary, and he was sent to the United States in August of that year. He was much emaciated and particularly dehydrated.

Examination—The blood pressure was 105, systolic, and 60, diastolic, general abdominal tenderness was present. The liver and spleen were not palpable, and the nervous system was reported normal. The mouth and esophagus were extremely sore. Bulky stools showed faulty digestion of fat, the gastric contents were usually achylic. The peripheral arteries were hard.

Laboratory examination gave the following results:

The Wassermann reaction was negative, and the urine was normal. A blood count on April 22, 1924, showed red cells, 2,100,000, hemoglobin, 60 per cent, white cells, 6,000. There was marked anisocytosis and poikilocytosis, and many macrocytes and microcytes. The stools showed many fatty acid crystals and globules of fat. The cultures were negative for *Moula*.

On Aug 3, 1924, the blood count was red cells, 1,840,000, hemoglobin (Dare), 35 per cent, white cells, 5,800. There was marked polychromatophilia.

The contents of the stomach in fasting did not show any free hydrochloric acid and the total acid was 2.

Treatment and Course—The patient was placed on a liberal diet of fruit and vegetables, and while there was some lessening of pain, diarrhea persisted, and he had fever at times. He later gained about 17 pounds (7.7 Kg) on a diet of oatmeal and soup. This improvement was temporary, and he was finally reduced to a milk diet, in spite of which diarrhea continued. The blood transfusions failed to influence the blood picture. He died on Oct 18, 1924. Autopsy was not performed.

CASE 6—History—C L W, a white soldier, aged 42, who had had nine years' service in the Philippines in three-year periods during the past seventeen years, had contracted malaria there in 1908, hookworm in 1912 and dysentery, probably bacillary, in 1917. He had been a steady user of alcohol and tobacco to excess. He was distinctly below par mentally, and a clear history of onset of the illness was not obtained. It is likely that he had had intermittent intestinal disturbance since the attack of dysentery in 1917, but it was not until January, 1925, that his commanding officer noticed that he was weak and obviously ill, and he was sent to the hospital in Manila. He had lost about 40 pounds (18.1 Kg) in weight, but he did not have pain and did not vomit or cough. In a few days he was transferred to the United States. It was noted that he had from three to four stools a day, tan colored at times, smooth, semisolid and free from gas, at other times they were liquid, yellow, foamy and contained some mucus. His only other symptoms were weakness and a daily afternoon rise of temperature.

Examination—Physical examination revealed pigmentation of the skin on the exposed parts and evidence of dehydration in dryness and loss of elasticity. The mucosae were pale and muddy. There was marked pyorrhea, the tongue was coated white, with beefy red margins.

The blood count showed red cells, 2,750,000, hemoglobin, 65 per cent, white cells, 11,400, polymorphonuclear, 82 per cent. Microcytes and poikilocytes were noted.

A tentative diagnosis of sprue was made, and calcium lactate was prescribed and later parathyroid extract and a diet of boiled milk and bananas. In spite of his indifference in following the diet, there was considerable improvement after a month. The stools became formed, he gained in weight and strength, and there was a lowering of the afternoon temperature.

Treatment and Course—A transfusion was performed shortly after he was admitted, and his blood picture improved considerably, the red cells increasing to 4,940,000 and the hemoglobin to 80 per cent. This was only temporary, however, for the hemoglobin dropped to 65 per cent a few days later.

It was soon discovered by physical signs, roentgenograms and positive sputum that he had an active pulmonary tuberculosis, and he was transferred to Denver. In the meantime, it was found that he had achlorhydria, and *Monilia psilosis* was isolated from his stools and from scrapings from his tongue. Neurologic examination was negative for changes in the cord.

The patient's subsequent history and the present status of his case is not known, for he left the hospital in Denver in December, 1925, after a few months of observation.

CASE 7—History—C. C. S., a white man, aged 50, who had lived thirteen years in the Philippines before being invalided home in June, 1926, had a definite alcoholic history. He had malaria in 1900, but there was no history of dysentery. The illness began rather suddenly in April, 1926, with sore mouth and diarrhea. He had five or six yellow, foamy stools during the day and as many at night. There was considerable asthenia, and his mouth was so sore that he was restricted to liquid diet. He entered a hospital in Manila, where a diagnosis of sprue was made. He received twenty doses of emetin, though there is no record of an amebic infection having been demonstrated. He was also given a course of treatment with calcium lactate and parathyroid. He had never had jaundice, but he had had some edema of the feet for two years prior to examination. He was 10 pounds (4.5 Kg.) underweight when he arrived in San Francisco, his tongue was glazed and swollen, with a few abrasions along the edges. The blood pressure was systolic, 100, and diastolic, 64. The abdomen was relaxed, the spleen was not felt, but there was slight tenderness over the gallbladder and the right kidney and considerable gas in the lower bowel. The cutaneous reflexes were exaggerated, and the muscles were hyperactive.

There was some improvement after he returned to the United States, the stools were firmer and fewer, edema of the feet disappeared, and the condition of the tongue improved, though it remained glazed and red. After a more liberal diet, diarrhea returned, and it was necessary again to restrict the patient to fresh fruits and vegetables. The lactate and parathyroid were continued, and he improved sufficiently to leave the hospital on Aug. 25, 1926. Since then we have not heard from him.

Laboratory Observations—The stools did not show mucus, blood or parasites on several examinations. On June 7, 1926, the blood count showed red cells, 2,850,000, hemoglobin, 55 per cent (Dare), white cells, 5,200, and polymorphonuclears, 56 per cent. On June 14, it was red cells, 2,100,000, hemoglobin, 50 per cent, white cells, 7,400, platelets, 165,400. The van den Bergh test gave negative results.

On July 5, the blood count was red cells, 2,400,000, hemoglobin, 60 per cent, reticulated cells, 1 per cent. The Wassermann reaction was negative.

The contents of the stomach did not show free hydrochloric acid during fasting, fractional specimens did not show free hydrochloric acid in the first three, 16 and 11 in the fourth and fifth, respectively. The total acidity varied from 11 to 38 cc.

A culture from the tongue was negative for *Monilia*.

CASE 8—*History*—J J O'B, a white man, aged 56, who had served six and a half years in the Philippines, where he had amebic dysentery in 1900 to 1901, had been a heavy drinker until 1912, but had been temperate since then. He said that he had had good health generally until 1922, when he began to vomit after meals and to have diarrhea. He lost 36 pounds (16.3 Kg) in weight in a few months. He was hospitalized for more than a year, during which time he was on a diet low in carbohydrates and fats, and he gained 40 pounds (18.1 Kg). During this admission, it was noted that his tongue was bright red and smooth, the deep reflexes increased, acids in the stomach were reduced, the blood pressure was 80 systolic and 60 diastolic, and he was anemic. He was discharged in August, 1923, but soon regressed on improper diet, returned to the hospital and stayed until October, 1924. He regained lost weight and was having one solid stool a day when he left. From November, 1924, however, he had been steadily losing in weight and strength. He had an average of ten watery, yellowish, foamy, bubbling, copious stools a day, he had lost his appetite, and when diarrhea was worst, his tongue was sore. He came under observation again in March, 1926, when he had lost 30 pounds (13.6 Kg) in weight and was anemic. The blood pressure was 90 systolic, and 70 diastolic, and the arteries were markedly sclerosed. He did not respond to treatment, and one transfusion made no impression on the blood picture. His stools were examined many times during the four years of observation and were invariably negative for parasites and *Monilia*, but there was usually evidence of poor digestion of fat. Several roentgenograms of the gastro-intestinal tract failed to reveal any pathologic condition. The Wassermann reaction was negative. At no time during this period was there any fever. For a period of about eight months, beginning in June, 1923, he suffered from neuritis involving both brachial plexuses. During the four years, his condition was variously diagnosed pernicious anemia, gastric ulcer, chronic dysentery and finally sprue.

The first blood picture on record is dated April 13, 1922. It is obvious that the anemia antedates this, and it is a question whether it was not well established when the gastro-intestinal symptoms appeared. The following is a chronologic record of the examinations of his blood.

On April 13, 1922, the count was red cells, 2,760,000, hemoglobin, 60 per cent. Considerable poikilocytosis was noted, and "platelets diminished."

On May 25, 1922, the blood showed red cells, 1,820,000, hemoglobin, 60 per cent, marked anisocytosis and poikilocytosis, but no nucleated red cells, white cells, 2,800, polymorphonuclears, 28 per cent. In July, 1922, it showed red cells, 3,460,000, hemoglobin, 75 per cent, in October, 1922 red cells, 4,510,000, hemoglobin, 80 per cent, in December, 1924 red cells, 3,100,000, hemoglobin, 65 per cent, and in April, 1926 red cells, 2,140,000, hemoglobin, 70 per cent. At this time he had an icterus index of 6.9 and a positive indirect Van den Bergh reaction.

In June, 1926, the count was red cells, 2,600,000, hemoglobin, 65 per cent, in September, 1926 red cells, 1,150,000, hemoglobin, 40 per cent, in November, 1926 red cells, 1,050,000, hemoglobin, 20 per cent, and in December, 1926 red cells, 870,000, hemoglobin, ?

He died on Jan 14, 1927, and the pertinent autopsy observations were as follows. The body was extremely emaciated and there were numerous petechiae on the dorsal surfaces of both hands. All intra-abdominal lymph nodes were moderately enlarged. The mucosa of the small intestine was moderately congested, but otherwise not remarkable. Lymph elements could not be distinguished in the ilium. The mucosa of the colon was perfectly smooth, the wall thin and anemic. The spleen was small. The bone marrow was pure yellow, and histologically it did not show any attempt at hemopoiesis. There was considerable hemosiderin in the liver cells. Bronchopneumonia was the immediate cause of death. The central nervous system was not examined.

SUMMARY

The pertinent features of the eight cases described are more clearly presented in the following summary

1	Personal History—(a)	Tropical residence	7
	(b)	Sex, males	8
	(c)	Age, 42-47, 2, 50-59	6
	(d)	History of dysentery	3
	(e)	History of alcohol	3
2	Onset—(a)	Diarrhea	5
	(b)	Sore mouth	1
	(c)	Indigestion	2
3	Symptom Distribution—(a)	Sore mouth	8
	(b)	Achlorhydria	7
	(c)	Diarrhea	8
	(d)	Anemia	8
		Remittent	5
		Progressive	3
	(e)	Central nerve symptoms	3
	(f)	Peripheral nerve symptoms	2
4	Predominant Complex—(a)	Gastro-intestinal, anemia and nervous	3
	(b)	Gastro-intestinal and anemia	4
	(c)	Gastro-intestinal	1
5	Duration in 4 patients who died—No	1, 3 years	
		No 4, 6 months	
		No 5, 1½ years	
		No 8, 4½ years	
	Duration in 4 patients still living—No	2, 4 years	
		No 3, 6 years	
		No 6, 8 years	
		No 7, 4 months	

The whole group showed sore mouth and diarrhea as prominent features, though these symptoms were more or less remittent, and, while diarrhea usually occurred first, sore mouth usually developed early and was more or less synchronous with diarrheal episodes. A definite anemia of pernicious type was seen in all, but it was impossible to place it in relation to the onset. This is a feature the patient could not determine himself, and it was usually not discovered until he had come under competent observation, but as it was usually well advanced, even in the cases seen shortly after onset of the obvious symptoms of the digestive tract, it is reasonable to assume that the "toxin" begins its attack on the blood in most cases early in the disease.

Seven of the cases showed a definite achlorhydria, the other one showed approximately 50 per cent reduction, and the majority showed evidence of pancreatic deficiency in the stools. This breakdown of the digestive function, in fact, is the most constant and striking feature of the disease. The fact that a number of patients give a history of "dysentery" may be significant, but it may as well be incidental in those cases

in which the diagnosis of dysentery is accurate. When the dysenteric diagnosis is not accurate, it may indicate, as does the digestive dysfunction, the onset of sprue and that the alimentary tract bears the brunt of the initial attack of the causative agents.

Sprue is preeminently a disease of white people in a tropical environment, in spite of exceptions to the contrary. The fact that in this group all the patients were men does not mean, of course, that the disease is confined to the male sex. We have seen several cases in women, but the data in their cases are not complete enough to include them. There is no doubt, however, that the disease occurs more commonly in men, perhaps because of their greater likelihood of contact with the etiologic factors. It is certainly a disease of adult life, not that clinical sprue does not occur in children, but the latter seem to be able to "come back" more completely and permanently under proper environment and are not so liable to the pernicious complex we are discussing.

The data presented would form little or no basis for a discussion of the etiology of the condition, and this will not be attempted, our idea is expressed simply as a hazardous conclusion.

One of us, during a three-year tour of duty in the Philippines, came in contact with a group of eleven cases which can be presented as a composite picture rather than individual cases partly because they were so similar and partly because in some instances the data are not sufficiently complete to warrant separate case reports. This group includes Americans and Englishmen and Spanish and Chinese mestizos, all with a long tropical residence, nine of them men, two women, and all well beyond middle age. They were seen in well advanced stages of anemia, and all died within a period varying from a few days to several months after coming under observation. The anemia was invariably aplastic in type and progressive in spite of all treatment. They all suffered from the digestive disturbances incident to achlorhydria, and they all gave a history of a previous intestinal phase in which they had suffered from persistent or sporadic diarrhea of from several months' to several years' duration, a feature that had usually been diagnosed chronic dysentery. In several of the cases, however, this condition persisted to the end, and we were able to study the character of the stools. They were the large, bulky, fermentative, foul discharges considered characteristic of sprue, free from any cellular or pathogenic content. In only one case was *Momilia* isolated, and then it was isolated from the blood by Dr. Smith, then professor of pathology in the medical school of the University of the Philippines. As a rule, however, the intestinal element had largely disappeared from the picture when the patients came under our observation, and the condition was being handled as anemia. It is not possible to speak of involvement of the nervous system in the cases, for the

patients were usually bedridden from asthenia when seen, and the previous history was not always reliable in regard to the subtle symptoms that indicate such involvement

CONCLUSIONS

1 There is a definite clinical entity, combining gastro-intestinal disturbances like those of sprue, an anemia approaching the so-called pernicious primary type and nervous phenomena characteristic of subacute myelonic degeneration of the spinal cord and of the peripheral nerves. Any combination of these groups may be found associated. We have described eight such cases under the heading of atypical sprue.

2 This variety of atypical sprue occurs chiefly in white men resident for varying periods in tropical or subtropical climates. This fact may account for the predominance of gastro-intestinal symptoms, in which it differs from Addisonian anemia. It is progressive, and, although remissions occur, the course usually proceeds to a fatal termination.

3 If it is assumed that these borderline or composite cases with polysystemic damage are the result of a single type of toxin of gastro-intestinal origin, it seems reasonable to suppose that classic sprue, Addisonian anemia or myelonic degeneration may have a similar etiology, and at times develop into this pleomorphic picture.

SERUM BILIRUBIN IN HEALTH AND IN DISEASE [†]

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CINCINNATI

In recent years, interest in jaundice has been largely transferred from the color of the skin and the presence or absence of bile pigment in the urine and feces to the changes occurring in the blood serum, much in the same way that physicians have become concerned with the urea content of the blood in nephritis, and with the concentration of blood sugar in cases of diabetes mellitus. The introduction of new and more delicate methods for the detection and estimation of bilirubin in the serum is responsible for this change in point of view. Perhaps the most notable method has been that of Hijmans van den Bergh of Utrecht, Holland,¹ popularized among the English speaking peoples by the publications of McNee of the University College of London.²

Estimations of serum bilirubin are necessary for the detection of potential or latent and also of transient states of jaundice, for the bilirubin content of the blood must reach a certain concentration before bilirubinuria³ occurs, and contact with the tissues must take place for a period of time before they assume a yellow color (Frerichs,⁴ van den Bergh⁵). Transient jaundice, unaccompanied by bilirubinuria or icterus of the tissues, occurs in attacks of gallstone colic (Meulengracht,⁶ van den Bergh⁵). Latent states of jaundice are present in patients receiving arsphenamine (Gerrard⁷) and frequently in pernicious anemia

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1 Van den Bergh, A. A. Hijmans. *Der Gallenfarbstoff Im Blute*, Leyden, 1918. Van den Bergh, A. A. Hijmans, and Snapper, J. *Deutsches Arch f klin Med* **110** 540, 1913. Van den Bergh, A. A. Hijmans. *Presse med* **29** 441, 1921.

2 McNee, J. W. *Brit M J* **1** 716, 1922, *Quart J Med* **16** 390, 1923. McNee, J. W., and Keefer, C. S. *Brit M J* **2** 52, 1925.

3 Van den Bergh (footnote 1, reference 1) has found this level (renal threshold) to be 2 mg in cases of obstructive jaundice. This has been substantiated by a number of authors (McNee) and is confirmed in this study. Andrewes found it to be usually around 1.75 mg. The kidneys are apparently impermeable to the bilirubin, giving only an indirect reaction (Andrewes. *Quart J Med* **18** 19, 1924).

4 Frerichs, F. T. *A Clinical Treatise on Diseases of the Liver*, trans by Murchison, C. **1** 66, 1879.

5 Van den Bergh (footnote 1, reference 1).

6 Meulengracht, E. *Demonstration of Transient Jaundice in Gallstone Colic*, *Arch Int Med* **35** 214 (Feb.) 1925.

7 Gerrard, W. I. *Brit M J* **1** 224, 1924.

(van den Bergh,⁵ Lepehne⁸ et al), and in malignant metastases to the liver (Greene et al⁹) Once the tissues become stained with the bile pigment (van den Bergh⁵), which they hold for a definite period of time, it follows that their color may not always be a true index of the degree of jaundice present, in contrast to the level of serum bilirubin. Determinations of the bilirubin content of the blood help to distinguish yellowish discolorations of the skin due to it from those due to other pigments, e g, carotin or lutein. By means of the van den Bergh technic, increases in serum bilirubin due to "obstructive" lesions which give prompt or direct reactions are differentiated from those occurring in "hemolytic" diseases which give delayed or indirect reactions (Lepehne,⁸ McNee¹⁰ et al). Lastly, the amount of bile pigment present in the blood may afford some idea, especially when it is abnormally increased, of the functional integrity of the liver, in the light of the recent work of Mann and his associates,¹¹ according to which bilirubin is formed chiefly in the bone marrow and spleen and is apparently primarily excreted, though formed to a slight extent, by the liver. It has been found that some parallelism exists between the degree of bilirubinemia and the retention of dyes of the halogen-phthalein series known to be excreted by the liver (Snell et al¹²).

The bile pigment content of the blood in the following study was estimated by the van den Bergh method, the original technic being employed¹³ in cases showing a delayed (more than one minute) or indirect reaction, the principle of Thannhauser and Andersen¹⁴ was employed in cases showing a prompt reaction,¹⁵ the original iron rhodionate solution of van den Bergh being employed as a quantitative

8 Lepehne, G. *Deutsches Arch f klin Med* **132** 96, 1920, **135** 79, 1921

9 Greene, C H, McVicar, C S, Walters, W, and Rowntree, L G. *Diseases of Liver, Arch Int Med* **36** 542 (Oct) 1925

10 McNee (footnote 2, second reference)

11 Mann, F C, Bollman, J L, and Magath, T B. *Am J Physiol* **69** 393, 1924. Mann, F C, Sheard, C H, and Bollman, J L. *Ibid* **74** 49, 1925. Mann, F C, Sheard, C H, Bollman, J L, and Baldes, E J. *Ibid* **74** 497, 1925, **76** 306, 1926, **77** 219, 1926.

12 Snell, A M, Greene, C H, and Rowntree, L G. *Diseases of Liver, Arch Int Med* **36** 273 (Aug) 1925

13 The qualitative and quantitative technic in which only a delayed or indirect reaction is obtained is given by McNee (footnote 2, second reference) or Ravdin (*Am J M Sc* **169** 850, 1925)

14 Thannhauser, J S, and Andersen, E. *Deutsches Arch f klin Med* **137** 179, 1921

15 The method consists of 1 cc of serum + 0.5 cc of diazo reagent + (after five minutes) 1 cc saturated solution of ammonium sulphate + 5 cc of alcohol (96 per cent). This is centrifugalized at high speed. The supernatant liquid is read against the standard. The dilution factor is 7.5. Greene (personal communication to the author) uses double the quantity of ingredients, 2 cc of serum + 1 cc of reagent, etc.

standard That no difference in the quantitative readings in cases showing only an indirect or delayed reaction occurs whether van den Bergh's original method or that of Thannhauser and Andersen is used was noted by the last named and was also determined in this study The readings are designated in milligrams per hundred cubic centimeters of serum, as others have done, instead of the unit or 1 in 200,000 parts of serum originally designated by van den Bergh, 0.5 mg per hundred cubic centimeters being the equivalent of 1 unit As some difficulty was experienced in making readings of less than 0.2 mg per cent, these are all designated as —0.2 mg per cent As it has been found, as was emphasized by Lepehne,⁸ that serum bilirubin tends to diminish on standing, because of oxidation to biliverdin, estimations were made within from one to two hours after the blood was obtained Specimens kept in the dark and on ice show practically no diminution over night No differences in the readings were noted whether plasma or serum was used, as others have experienced¹⁶

Biphasic reactions described by Feigl and Querner¹⁷ have been included under the direct reactions for reasons similar to those of Andrewes (McNee and Keefer²) It is felt that they represent quantitative transitions between the indirect and the direct reactions, having been encountered early in experimental ligation of the common duct and late in cases of catarrhal jaundice in the course of this study Greene also does not consider such a reaction separately¹⁸

NORMAL SERUM BILIRUBIN

The van den Bergh reaction was applied to the blood of 202 "normals" of the following age groups

From 5 months to 9 years	11
From 10 to 19 years	11
From 20 to 29 years	101
From 30 to 39 years	28
From 40 to 49 years	24
From 50 to 59 years	20
From 60 to 69 years	7

The group of normals was composed of 112 medical students, interns and nurses in good health (most of whom had had a recent physical examination), twenty-six individuals above 30 years of age found to be normal at the Pay-Health Clinic conducted under the auspices of The United Jewish Social Agencies, forty-six inmates of

¹⁶ McNee (footnote 2, second reference) Ravdin, E. G. *Am J M Sc* **169** 850, 1925

¹⁷ Feigl J., and Querner, E. *Ztschr f d ges exper Med* **9** 153, 1919

¹⁸ Greene, C. H. Personal communication to the author

Longview Hospital for the Insane (twenty-seven males, nineteen females), normal physically but affected with a psychosis other than alcoholic, twelve children, five in the pediatric service of the Cincinnati General Hospital for gonorrheal vaginitis, five at the Branch Hospital for Tuberculosis on account of a "contact history," and two examined in private life, and six relatives of the four individuals giving the highest values

In 193, or 95.54 per cent of the normals, the value of serum bilirubin was less than 0.6 mg, in six, or 2.97 per cent, it was between 0.6 and 0.9 mg, and in three, or 1.49 per cent, between 1.0 and 1.5 mg. The relative values in the two sexes and the total percentage frequency of any given value or less are illustrated in table 1.

This table would indicate that the level of serum bilirubin is relatively higher in males than in females, for in thirty, or 47 per cent, of

TABLE 1—*Relative Values and Total Percentage Frequency of Any Given Value or Less*

Mg Bilirubin*	Per Cent Males	Per Cent Females	Total per Cent Having Given Value or Less
—0.2	28.2	47.0	34.15
0.2–0.29	30.4	26.5	63.36
0.3–0.39	19.0	14.0	80.69
0.4–0.49	8.7	8.0	89.1
0.5–0.59	8.7	1.5	95.54
0.6–0.69	0.0	1.5	96.03
0.7–0.79	2.1	1.5	98.01
0.8–0.89	0.72	0.0	98.51
0.9–0.99	0.0	0.0	
1.0–1.5	2.1	0.0	100.0

* Blood taken from one to four hours after a meal. The value of milligrams of bilirubin denotes the amount per hundred cubic centimeters of serum. The reactions were all indirect.

the females, the bilirubin value was less than 0.2 mg in contrast to thirty-eight or 28.2 per cent of the males, and in three females, or 4.5 per cent, above 0.5 mg, in contrast to nineteen males, or 13.6 per cent above this level. The four values above 0.8 mg were limited to the males. No distinct differences were observed in the various age groups. The blood from the umbilical cord of thirteen new-born infants was examined in addition, and the physiologic hyperbilirubinemia described by van den Bergh and others was encountered, the readings being in the vicinity of 1 mg or more.

That the value of the serum bilirubin is not absolutely constant was first shown by Gilbert and Herscher,¹⁹ who found it to increase somewhat during fasting. The blood of three of the normal individuals here studied was examined daily before breakfast for one week, a maximum variation of 0.2 mg being noted. Forster and Forstner,²⁰ who exam-

¹⁹ Gilbert and Herscher. *Presse méd.*, 1906, no. 27, quoted by van den Bergh.

²⁰ Forster, J., and Forstner, B. *Ztschr. f. klin. Med.* 103:703, 1926.

med eighteen individuals with various diseases under the foregoing conditions, employing the technic of Ernst and Forster,²¹ found a variation generally between 0.1 and 0.3 mg. On examining twenty-one individuals before breakfast, two hours after the noon meal, and before the evening meal, they found the highest values generally, but not always, before breakfast. The fluctuations were generally from 0.1 to 0.2 mg. Broun et al.²² found a variation of as high as 0.5 mg. in a normal individual, the blood being taken before breakfast, before dinner (12.00) and at 4.00 p. m. According to Meyer and Knupffer,²³ the blood bilirubin diminishes in quantity from two to five hours after meals, and increases after eight hours, apparently on the basis that during digestion bilirubin is excreted from the blood (Forster and Forstner).

As 98 per cent of the normal patients had a value of approximately 0.8 mg. or less, 1 mg. may be safely considered the upper limit of normal, thus allowing 0.2 mg. for fluctuation during the day and from day to day. As a value of 0.6 and 1 mg. was exceeded in only 4.5 per cent of the cases, any value between 0.6 and 1 mg. should be considered as possibly indicative of an increase, particularly as the latter figure is approached. In his monograph, van den Bergh²⁴ states that in the vast majority of healthy individuals the values found are between 0.25 and 0.4 mg. (from 1 to 400,000 to 1 to 250,000). In a later paper published in France,²⁵ he gives figures for the bilirubin content of normal human serum of from 0.1 mg. to 0.25 mg. (1,000,000 to 1,400,000), which have been accepted by Lepehne, McNee, Ravdin et al. Lepehne⁸ found the average figure in a series of patients not suffering from jaundice to be 0.15 mg. McNee¹⁰ obtained similar results. Botzian²⁶ and Wiemer²⁷ also consider the upper limit of normal 0.75 mg., Mandelbaum,²⁸ 0.62 mg. (1.25 units) and Haselhorst,²⁹ 0.5 mg. (1 unit). Strauss and Buerkmann³⁰ found values between 0.15 and 0.55 mg. in fifty normal patients, with an average of 0.3 mg. Forster and Forstner consider 1 mg. as the upper limit of normal. Greene and his

21 These authors add to 1 part of serum, 1 or 2 parts of colorless acetone, they then centrifugalize it and compare the supernatant liquid with a standard solution of potassium chromate, 1/6,000.

22 Broun, G. O., Ames, O., Warren, S., and Peabody, F. W. *J. Clin. Investigation* **1** 295, 1924-1925.

23 Meyer, E. C., and Knupffer, H. *Deutsches Arch. f. klin. Med.* **138** 321, 1922 (Forster and Forstner).

24 Van den Berg (footnote 1, reference 1).

25 Van den Bergh (footnote 1, reference 2).

26 Botzian, R. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **32** 549, 1920.

27 Wiemer, P. *Deutsches Arch. f. klin. Med.* **151** 154, 1926.

28 Mandelbaum, R. *Monatschr. f. Geburtsh. u. Gynak.* **59** 17, 1922.

29 Haselhorst, G. *Munchen med. Wchnschr.* **68** 174, 1921.

30 Strauss, L., and Buerkmann, W. *Klin. Wchnschr.* **1** 1407, 1922.

co-workers³¹ at the Mayo Clinic consider 2.0 mg as the maximum normal. This limit takes care of instances of familial cholemia.

Particular attention was paid to the four individuals (medical students) with the highest values of serum bilirubin—0.8, 1.1, 1.25 and 1.5 mg, respectively—who represent what Gilbert and Lereboullet,³² in 1906, called simple familial cholemia and what van den Bergh spoke of as physiologic hyperbilirubinemia. In all four there was a yellowish cast to the skin, and the periphery of the sclerae was slightly icteric. In none was the liver or spleen felt. None had ever noticed or had ever been told that he was distinctly jaundiced, except patient 4, who on one occasion, two years ago, had been told that his skin was yellow. There was no instance of unexplained priapitis or definite bradycardia. The specimens of urine were entirely normal, except for the presence of urobilin in traces in two of the individuals and in marked excess in the other two. A questionable increase in erythrocytic fragility was noted.

TABLE 2—Data of Four Patients Having Highest Serum Bilirubin

No	Mg Bilirubin	Icterus Index*	Red Blood Cells	Per Cent Hemo-globin	Per Cent Reticulated Cells	Urobilinuria	Erythrocytic Fragility†	Retention of Bromsulphalein‡
1	1.5	14	6,400,000	93	0.25	++	0.44-0.36	0
2§	1.25	11	6,000,000	85	0.2	Trace	0.44-0.36	0
3	1.1	12	5,600,000	90	1.0	++	0.42-0.36	0
4	0.8	9	6,000,000	85	0.1	Trace	0.44-0.36 0.42-0.34 (control)	0

* Method of A. R. Bernheim (Icterus Index, J. A. M. A. **82**: 291 [Jan. 26] 1924).

† Technic of Griffin and Sanford (J. Lab. & Clin. Med. **4**: 465, 1918-1919).

‡ Retention in one half hour. Technic of Rosenthal and White (Clinical Application of Bromsulphalein Test for Hepatic Function, J. A. M. A. **84**: 1112 [April 11] 1925).

§ Jewish patient.

in one. A relatively high red cell count was present in three. Van den Bergh²⁴ has occasionally encountered a palpable spleen in addition to urobilinuria in similar cases and feels that such cases border on chronic hemolytic jaundice. He found the disease more common among the Jewish race and generally encountered values of 1.1 and 1.25 mg.

The observations in the four individuals are tabulated in table 2.

OBSERVATIONS IN DISEASE

1 *Congestive Heart Failure*—There were twenty-three cases of congestive heart failure—five rheumatic (four mitral lesions and one adherent pericardium), five syphilitic (aortic insufficiency), five hypertensive, six arteriosclerotic, one mitral and tricuspid insufficiency (etiology?) and one of auricular fibrillation associated with a toxic thyroid adenoma (table 3).

31 Greene, C. H., Snell, W. M., and Walters, W. Diseases of Liver, Arch. Int. Med. **36**: 248 (Aug.) 1925.

32 Gilbert, A., and Lereboullet, P. Compt. rend. Soc. de biol. **58**: 937 and 1007, 1905, quoted by van den Bergh.

The higher values were more frequently encountered in the initial lesions, an experience similar to that of Fishberg³³ and of Meulengracht,³⁴ the latter author using the icterus index. In eleven patients, the values were 0.65 mg or below, of these, nine improved and two died. Of five with a value between 1.0 and 1.35 mg, two were improved and three died. The remaining readings were above 2.0 mg (five direct increases and two indirect increases), both of the patients having indirect increases and three having direct increases died. The highest value obtained was 4.6 mg in a case that proved fatal. No bilirubinuria was present in the two patients giving an indirect increase, while bilirubinuria was present in the five giving the direct reaction, there was thus a virtual hemolytic and obstructive type of jaundice present.

TABLE 3—*Congestive Heart Failure*

No	Age	Liver (Right Midclavicular Lane)	Red Blood Cells	Hemo- globin, per Cent	Jaun- dice	Died	Mg Bilirubin		Etiology
							Direct	Indirect	
1	27	10 cm	5,100,000	70	+	+	2.25	—	Rheumatic
2	30	6 cm	4,400,000	90	+	+	2.8	—	Rheumatic
3	42	10 cm	4,200,000	60	+	+	—	2.5	Rheumatic
4	16	4 cm	4,400,000	70	—	+	—	2.5	Rheumatic
5	32	Edge	5,800,000	90	—	—	—	1.0	Rheumatic
6	48	10 cm	4,100,000	70	—	—	—	0.5	Syphilitic
7	43	—	3,800,000	70	—	—	—	0.3	Syphilitic
8	48	10 cm	5,300,000	70	—	—	—	0.25	Syphilitic
9	49	10 cm	4,200,000	70	+	+	4.6	—	Syphilitic
10	32	4 cm	4,000,000	80	+	—	3.0	—	Syphilitic
11	52	6 cm	3,600,000	80	—	—	—	1.25	Hypertensive
12	64	8 cm	4,100,000	70	—	+	—	1.0	Hypertensive
13	57	6 cm	4,900,000	90	—	—	—	0.5	Hypertensive
14	56	—	5,000,000	80	—	+	—	0.65	Hypertensive
15	41	10 cm	5,400,000	80	—	+	—	1.0	Hypertensive
16	60	—	5,400,000	80	—	—	—	0.5	Arteriosclerotic
17	61	—	3,900,000	70	—	—	—	—0.2	Arteriosclerotic
18	72	—	4,500,000	90	—	—	—	0.25	Arteriosclerotic
19	58	—	5,200,000	80	—	+	—	0.4	Arteriosclerotic
20	62	—	3,900,000	70	—	—	—	—0.2	Arteriosclerotic
21	65	4 cm	4,700,000	94	+	—	2.5	—	Arteriosclerotic
22	43	10 cm	5,700,000	80	—	+	—	1.35	Mitral and tricuspid insufficiency
23	68	—	4,300,000	80	—	—	—	0.3	Toxic goiter (auricu- lar fibrillation)

Sections of the livers of the two patients with the hemolytic type of jaundice and of two with the obstructive type were examined by Dr. Richard Austin, but they did not reveal any especial difference in the pathologic picture. All presented a chronic passive congestion with hemorrhage. None of the cases showed demonstrable pulmonary infarcts, their relationship to the jaundice occurring in myocardial insufficiency has been noted by a number of authors (Eppinger,³⁵ Libman,³⁶

33 Fishberg, A. M. Jaundice in Myocardial Insufficiency, J. A. M. A. **80** 1516 (May 26) 1923

34 Meulengracht, E. Deutsches Arch. f. klin. Med. **132** 285, 1920

35 Eppinger, H., in Kraus and Brugsch. Handb. d. spez. Path. u. Therap. **6** 293, 1923

36 Libman, cited by Fishberg (footnote 33)

Keefer and Resnik³⁷ and Rich and Resnik³⁸) In two instances of jaundice developing after pulmonary infarction, Keefer and Resnik obtained a direct reaction of 2.5 mg

The mortality in the foregoing cases appears to be directly proportional to the height of the serum bilirubin, an experience similar to that of Bernheim³⁹ and others, as shown in table 3

Thus, in virtually one out of five cases with a value of less than 1.0 mg the outcome was fatal, in contrast to two out of three with a value of 1.0 and more

In nine of twelve cases showing definite hepatic enlargement, the value of the serum bilirubin was 1 mg or over. However, the remaining three patients (two with the liver 10 cm below the costal margin),

TABLE 4—*Proportion of Mortality to Height of Serum Bilirubin*

Mg Bilirubin	Number Cases	Mortality
Less than 1.0	11	18.1
1.0 and over	12	66.6

TABLE 5—*Acute Alcoholism*

No	Mg Alcohol per Cc of Urine*	Coma	Mg Bilirubin Indirect
1	4.2	+	—0.2
2	3.9	++	—0.2
3	4.3	+	0.2
4	2.0	+	—0.2
5	3.0	+	0.4
6	5.0	+	—0.2
7	4.5	+	0.25
8	5.0	+	—0.2
9		+	—0.2
10	3.9	+	—0.2
11	5.0	+	—0.2
12	3.0	—	—0.2

* Determinations by Dr. E. Bagen

who had a value of only 0.6 mg or less, all recovered, thus illustrating the fact that hepatic enlargement does not necessarily signify retention of bilirubin, similar results have been noted by Fishberg³³ and Andrews^{39a}. There was no instance of definite hyperbilirubinemia in the eight cases that did not show enlargement of the liver. Brulé⁴⁰ and Fishberg, however, have noted such an increase in the absence of hepatic enlargement in cases of cardiac decompensation. Lepehne⁸ and Fishberg³³ have noted that the high values of blood bilirubin occurring in cardiac insufficiency are lowered with an improvement in compensation.

37 Keefer, C. S., and Resnik, W. H. *J. Clin. Investigation* **2**: 375 and 389, 1926

38 Rich, A. R., and Resnik, W. H. *Bull. Johns Hopkins Hosp.* **38**: 75, 1926

39 Bernheim, A. R. *Icterus Index*, *J. A. M. A.* **82**: 291 (Jan. 26) 1924

39a Andrewes, C. H. *Quart. J. Med.* **18**: 19, 1924

40 Brulé, M. *Recherches sur les ictères*, Paris, ed. 3, 1922, p. 117

2 *Acute Alcoholism*—In twelve cases of acute alcoholism, an increase in the serum bilirubin was not encountered, but, on the contrary, a tendency toward hypobilirubinemia was noted (table 5). In four of the cases (5, 6, 7 and 8), blood counts and determinations of volume index were made to exclude hydremia and anemia. In cases 5 and 7, the determinations were repeated twelve hours later, with virtually the same results. Whether the patients' levels of serum bilirubin were low before the ingestion of alcohol or whether alcohol stimulates the liver to increased excretion of bilirubin is not known.

3 *Tabes Dorsalis*—No increase was noted in the serum bilirubin during gastric crisis in three cases of tabes dorsalis (table 6). This

TABLE 6—*Tabes Dorsalis with Gastric Crisis*

No	Mg Bilirubin Indirect	Comment
1	—0.2	During crisis
2	—0.2	During crisis
3	—0.2	During crisis

TABLE 7—*Lobar Pneumonia with Jaundice*

No	Age	Lobes Affected	White Blood Cells	Red Blood Cells	Hemo- globin, per Cent	Day of Illness	Day of Jaun- dice	Mg Bilirubin Direct
1	23	Right lung	63,000	3,600,000	70	9	?	8.0
2	33	Right middle and lower	12,000	4,600,000	90	9	2	10.7
3	20	Right lung, left lower	17,000	3,000,000	80	8	?	6.3
4	31	Right upper	9,400	2,700,000	65	8	4	4.3
5	34	Right upper	25,000	—	40	7	4	10.0
6	20	Both lower especially right, left apex, slightly	21,400	4,900,000	90	30 hrs	?	4.7
7	39	Right lower	10,000	—	—	8	?	10.6
8	33	Right lower	18,600	4,100,000	70	6	?	11.0
9	19	Right lung and left lower	28,300	4,400,000	100	12	3	10.0
10	38	Right lung	16,400	—	—	7	?	3.7
11	31	Right lung	26,000	4,100,000	60	4	?	5.0
12	24	Right upper	29,000	4,500,000	—	8	?	5.0
13	22	Right lower	13,300	4,200,000	90	6	?	14.0
14	40	Left upper, later right upper	21,000	4,400,000	90	10	1	4.0

observation should be of value in differentiating such a crisis from an attack of gallstone colic. According to Meulengracht,⁶ there is also not any rise in the serum bilirubin during attacks of renal colic or acute appendicitis.

4 *Acute Lobar Pneumonia (with Jaundice)*—In fourteen cases of jaundice developing in the course of acute lobar pneumonia, the most striking observation was the involvement of one or more lobes of the right lung in thirteen cases, and while the left upper lobe was infiltrated at the time of the onset of jaundice in the fourteenth case, infiltration of the right upper lobe subsequently occurred (two weeks later) (table 7). In the thirteen cases in which the right side was involved, there was associated involvement of the left lower lobe in two cases and slight infiltration of the left apex in the third. Of seven more

patients having pneumonia with jaundice on whom estimations of serum bilirubin were not done, the process was limited to the right side in four, it was present on both sides in two, and in the seventh, while originally present on the left side (lower, then left upper), subsequently involved the right lower lobe twelve days later

Thus, in 21 cases of acute lobar pneumonia showing jaundice, among a total of 826 patients having lobar pneumonia admitted to the hospital between 1923 and 1926, inclusive, the pneumonic process was present on the right side in all, in two of the cases (initially left-sided), the jaundice preceded recognizable infiltration of the right side. While the constant association of jaundice and pneumonia on the right side occurring in this group of cases may be coincidental, it suggests the possibility of an anatomic basis as a factor in the production of the secondary infectious hepatitis of pneumonia.

Eight of the twenty-one patients died, bearing out Cole's statement ⁴¹ that the occurrence of jaundice in acute lobar pneumonia is not of serious prognostic significance.

TABLE 8—*Chronic Hemolytic Jaundice*

No	Duration Jaundice	Gall- bladder Disease	Abdom- inal Pain	Spleen Enlarged	Red Blood Cells	Hemo- globin, per Cent	Fragility Increase	Mg Bilirubin Indirect
1	8 years	+	+	—	4,800,000	80	—	5.0
2	10 years	+	+	4 cm	4,800,000	80	—	7.5
3	10 years	±	—	4 cm	3,900,000	65	+	5.6
4	9 years	+	—	—	2,600,000	50	+	2.8
5	3 years	—	—	Edge	4,600,000	90	+	2.5

The earliest instance of marked hyperbilirubinemia was thirty hours after the onset of the disease (case 6), in which a value of 4.7 mg was found approximately twenty-four hours prior to the occurrence of bilirubinuria.

5 *Chronic Hemolytic Jaundice*—All of the cases presented a definite increase in the percentage of the reticulated cells, with marked urobilinuria (slight in case 4), and absence of bile salts and pigment from the urine (table 8).

Only an indirect reaction was obtained, as van den Bergh first pointed out, regardless of the degree of bilirubinemia.

That there is no direct relationship between the fragility of the red cells and bilirubinemia is borne out in cases 2 and 5, several simultaneous determinations being made in the latter (table 9). It is noteworthy that within seventy-two hours after splenectomy the serum bilirubin in this case dropped from a level of 4.2 to 0.35 mg—an experience similar to that reported by Rich and Rienhoff ⁴².

• 41 Cole, R., in Nelson's Loose-Leaf Living Medicine 1 203, 1924.

42 Rich, A. R., and Rienhoff, W. F., Jr. Bull. Johns Hopkins Hosp. 36 431, 1925.

Evidence of disease of the gallbladder was present in 3, or 60 per cent of the series, a fact in harmony with the observations of W J. Mayo⁴³ in a large series of cases. The evidence in cases 1 and 2 consisted of attacks of severe pain in the right upper quadrant and vomiting, with temporary increase in the jaundice plus failure to visualize the gallbladder by Graham's method. Gallstones had been found in case 4 eight years previously, when a cholecystotomy was performed. Patient 3 was operated on for supposed disease of the gallbladder and later for "adhesions," but he did not know what was found or done.

It should be noted that the highest bilirubinemia was encountered with a red cell count of 4.3 million. In the instance of the lowest red cell count (case 4), a value of only 2.8 mg was found, somewhat contrary to what one would ordinarily expect in this disease. However, the patient also had arterial hypertension with some renal involvement, and thus another factor may have been present in the production of the anemia.

TABLE 9—*Serum Bilirubin in Case 5*

	Date							
	Feb 11	March 17	May 11	May 14	May 14	May 17	Sept 3	March 14
Fragility pt	0.42-0.32	0.48-0.42	0.44-0.36		Sple-	0.48-0.38	0.44-0.36	0.40-0.32
Fragility control	0.42-0.32	0.42-0.34	0.40-0.32		nec		0.40-0.32	0.40-0.32
Mg bilirubin	2.5	1.0	3.1	4.2	tomy	0.35	1.7	2

The two highest values were obtained in the individuals showing the greatest splenic enlargement. The return of the hyperbilirubinemia in case 5 following splenectomy may be due to the existence of a simple familial cholemia, which van den Bergh hints may in some instances possibly be the forerunner of a hemolytic jaundice. It may be added that the diagnosis in this case was substantiated at the Mayo Clinic. Since splenectomy was performed, the patient has regained his former energy and is able to perform the arduous tasks of a resident surgeon. There has been only a trace of urobilin in the urine on a number of examinations, and the reticulated cell count has remained normal. If nothing were known of the patient's previous history, his case might well be taken for one of simple familial cholemia. It should be added that he has achlorhydria.

6 Sickie Cell Anemia—An indirect increase in the serum bilirubin, similar to that in chronic hemolytic jaundice and pernicious anemia as directly opposed to the results in most secondary anemias, would indicate that the anemia in this disease is hemolytic in character (table 10). In case 2, which showed the highest value in the series, bilirubinuria was not present but marked urobilinuria was found.

Splenectomy in one case did not effect a disappearance of the hyperbilirubinemia, nor of the "sickling" of the red cells. The latter is perhaps comparable to the persistence of increased erythrocytic fragility following splenectomy in chronic hemolytic jaundice.

The first two of my cases were reported by Alden,⁴⁴ while a report of the third is to be published by Mitchell⁴⁵ and his associates.

7 Hereditary Hemorrhagic Telangiectasia—In six patients who had hereditary hemorrhagic telangiectasia, a low value of serum bilirubin, similar to that obtained in ordinary secondary anemia, was present (table 11). Apparently, only mechanical loss of blood occurs in this disease.

TABLE 10—*Sickle Cell Anemia*

No	Age	Sex*	Color	Red Blood Cells	Hemoglobin, per Cent	Mg Bilirubin Indirect	Comment
1	4	♂	Black	2,500,000	69	1.0	
2	18	♂	Black	2,000,000	45	1.0	
3	2½	♂	Black	3,000,000	40	1.4	Splenectomy (Oct 30)
				2,700,000 (Oct 13)	80	0.65	
				4,000,000		(Nov 13) 1.0	
						(Dec 13) 1.3	
4	14	♀	Black	1,700,000	30		

* In this table and table 16, ♂ indicates male, ♀, female.

TABLE 11—*Hereditary Hemorrhagic Telangiectasia**

No	Red Blood Cells	Hemoglobin, per Cent	Mg Bilirubin Indirect
1	1,800,000	35	0.3
2	4,400,000		0.2
3	3,600,000	50	—0.2
4	3,800,000	65	0.3
5	4,200,000	75	0.2
6	4,800,000	70	—0.2

* Mother and five children affected.

8 Cirrhosis of the Liver—The series included sixteen cases, fourteen showing tertiary hepatic syphilis and two showing portal cirrhosis, probably alcoholic (table 12). The clinical diagnoses were based on the criteria set forth by Rolleston⁴⁶ and McCrae and Caven,⁴⁷ a number of cases being excluded because of insufficient evidence.

Eight of the sixteen patients showed neither jaundice nor increase in the serum bilirubin, while the other eight were jaundiced, five frankly so and three with bile tinged sclerae and mucous membranes, and with a questionable yellow tinge to the skin.

44 Alden, H. S. *Am J M Sc* **173**:168, 1927.

45 Mitchell, A. G., Bell, A. J., and Kotte, R. H. *Am J Dis Child*, to be published.

46 Rolleston, H. D. *Oxford Med* **3**:304, 1921.

47 McCrae, T., and Caven, W. R. *Am J M Sc* **172**:781, 1926.

Six of the eight patients without jaundice had experienced one or more hematemeses in the past and presented a severe degree of secondary anemia. In contrast, only one of the eight jaundiced patients had had a hematemesis prior to the occurrence of the jaundice, and in only two (patient 9 had vomited blood just prior to admission) did a severe secondary anemia exist. In five of the eight cases not showing jaundice,

TABLE 12—*Cirrhosis Hepatis**

No	Age	Hematemesis	Ascites	Liver (Right Midclavicular Line)	Spleen	Blood Wassermann Test	Pathologic Diagnosis	Red Blood Cells	Hemoglobin, per Cent	Jaundice	Mg Bilirubin	
											Direct	Indirect
1	43	+	+	14 cm	9 cm	4+	—	2,100,000	35	—	—	0.4
2	31	+	0	5 cm	4 cm	4+	—	2,800,000	50	—	—	0.45
3	42	+	+	4 cm	Edge	+	—	2,400,000	50	—	—	0.5
4	38	+	+	—	4 cm	4+	—	2,200,000	30	—	—	0.65
5	42	+	+	—	—	4+	+	2,500,000	—	—	—	0.3
6	56	+	—	—	—	—	—	2,900,000	50	—	—	—0.2
7	43	0	0	8 cm	Edge	—	+	4,700,000	90	—	—	—0.2
8	30	+	+	4 cm	2 cm	4+	—	2,300,000	35	+	+	—
9	44	0	+	8 cm	—	4+	+	2,900,000	55	+	2.5	—
10	41	0	+	8 cm	—	+	—	4,000,000	85	+	7.0	—
11	39	0	0	11 cm	8 cm	—	—	3,400,000	70	+	6.5	—
12	38	0	+	—	0	—	—	3,900,000	70	+	—	1.75
13	42	0	0	12 cm	0	—	+	4,800,000	80	+	—	1.5
14	60	+	0	—	—	—	+	3,700,000	45	+	2.5	—
15†	51	0	+	8 cm	4 cm	—	—	4,100,000	70	—	—	1.5
16†	55	0	+	—	—	—	+	4,000,000	70	+	—	1.5

* Cases 1 to 14 inclusive showed tertiary syphilis

† Portal (alcoholic) cirrhosis

TABLE 13—*Malignant Disease of the Liver*

No	Age	Liver (Right Midclavicular Line)	Red Blood Cells	Hemoglobin, per Cent	Primary Site	Mg Bilirubin		Jaundice	Pathologic Diagnosis
						Direct	Indirect		
1	73	10 cm	3,900,000	75	Stomach	—	0.3	—	+(N)*
2	65	4 cm	4,800,000	80	Breast	—	0.5	—	—(N)
3	35	11 cm	4,500,000	90	Pancreas	—	0.55	—	+(N)
4	71	10 cm	4,300,000	65	Stomach	—	0.75	—	—
5	81	4 cm	4,100,000	90	Stomach	—	0.25	—	—
6	48	2 cm	2,400,000	35	Stomach	—	0.25	—	+(B)†
7	26	4 cm	2,600,000	35	Stomach	—	—0.2	—	+(B)
8	57	15 cm	4,500,000	80	Gallbladder	—	—0.2	—	+(N)
9	47	6 cm	3,600,000	80	?	—	1.0	—	+(N)
			1,300,000	30	(Carcinoma)	—	—0.2	—	—
10	4½ mo		1,700,000	55	Liver (hepatoma)	—	0.6	—	+(N)
11	67	10 cm	4,000,000	85	Stomach	+	—	+	+(N)
12	45	11 cm	4,300,000	50	Pancreas	+	—	+	+(N)
13	56	10 cm	—	80	Undetermined	3.1	—	+	+(B)
14	70	15 cm	4,000,000	70	Bile duct	19.5	—	+	+(N)
15	69	4 cm	3,200,000	70	Gallbladder	15.0	—	+	+(B)
16	68	2 cm	—	75	Stomach	20.0	—	+	+(B)
17	66	Nodular	3,900,000	60	Iris	4.6	—	+	+(N)

* (N) indicates necropsy

† (B) indicates biopsy

a hyperbilirubinemia was absent, in spite of considerable enlargement of the liver. In three of these, a severe anemia existed. While it is realized "that more than three-fourths of the liver can be abruptly obstructed without causing even a ripple on the clinical surface of things" (Rous⁴⁸ and McMaster and Rous⁴⁹), a relationship of the

48 Rous, Peyton. Am J M Sc 170 625, 1925

49 McMaster, P. D., and Rous, Peyton. J Exper Med 33 731, 1921

level of the serum bilirubin as well as the occurrence of jaundice in cases of hepatic cirrhosis to the amount of circulating hemoglobin and blood cells appears to be suggested, as in the cases of hepatic malignant disease studied

9 *Malignant Disease of the Liver*—There were seventeen cases, seven with jaundice and ten without (table 13). Among those without jaundice, there were only two relatively high values, viz., 0.75 and 1 mg., the remainder being 0.6 mg. or less. In eleven cases of carcinoma of the liver without jaundice (diagnosis pathologically confirmed) Greene and his associates⁹ found two presenting bilirubin values above 2 mg. and three showing values between 0.9 and 1.6 mg., they feel that while the determination of serum bilirubin may not show any increase in some cases, it is nevertheless of definite value in the early diagnosis of carcinoma of the liver.

TABLE 14—*Acute Catarrhal Jaundice*

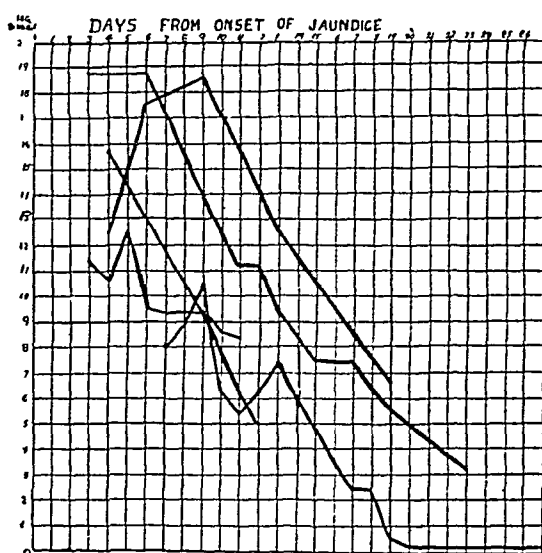
Number	Age	Liver (Right Midclavicular Line)	Spleen	Day of Jaundice	Mg. Bilirubin Direct
1	9	6 cm	0	9	6.5
2	25	0	0	10	10.0
3	6	0	0	4	7.0
4	40	9 cm	Edge on inspiration	21	4.0
5	37	1½ cm	0	6	15.6
				14	18.7
6	26	0	0	Day preceding	4.0
7	36	0	0	7	10.0
8	33	4 cm	0	24	2.7
9	15	2 cm	Edge	4	12.0
10	42	8 cm	0	25	3.0
11	19	2 cm	0	4	15.6
12	33	0	0	4	8.0
13	44	4 cm	Edge	2	18.7
14	17	6 cm	6 cm	7	9.4
15	44	5 cm	Edge	4	12.5

The absence of hyperbilirubinemia in the presence of hepatic malignant disease has also been noted by Lepehne,⁸ Meulengracht,³¹ and Andrewes.^{39a} In the four cases showing the lowest readings in bilirubin, a severe secondary anemia was present. In four of Greene's eleven cases in which the values were 0.2 mg. or less, a severe secondary anemia existed in three. On the other hand, it is of interest to note that a severe secondary anemia was not present in five of the seven cases showing jaundice in which counts were recorded, and in all fourteen of such cases reported by Greene.

It is of great interest to note a fall in serum bilirubin in one of the cases (carcinoma), accompanying a drop in the hemoglobin and in the number of red cells. Greene¹⁸ has also seen the serum bilirubin fall in malignant disease of the liver.

10 *Acute Catarrhal Jaundice*—Fifteen cases of acute catarrhal jaundice were studied, serial estimations being made from day to day in five (table 14). The mean value during the first week of jaundice was

approximately 13 mg—a deep jaundice, during the second week, an average of approximately 9 mg, a moderately deep jaundice, and during the third week, an average of approximately 4 mg, representing a relatively mild jaundice. In the light of these estimations, the mechanism of acute catarrhal jaundice appears frequently to be one of sudden marked disablement of the liver in regard to the excretion of bilirubin, lasting frequently for less than a week, with subsequent rapid resumption of function. This is in accord with the “two distinct phases” of the disease described by Jones and Minot⁵⁰ in an extensive study of twenty-six cases, who also found the concentration of serum bilirubin during the disease to be a reciprocal of the concentration of bile pigment in the duodenum.



Acute catarrhal jaundice

During the first week of jaundice, hepatic enlargement was detected in seven cases, an associated splenic enlargement being present in four instances. The average value of bilirubin in the three cases showing only hepatic enlargement was 13.06 mg, virtually the same as the average value in the four cases showing both splenic and hepatic enlargement (13.15 mg per cent). In sharp contrast to this is the average of 7.25 mg per cent in the four cases showing neither apparent hepatic nor splenic enlargement, in which determinations were also made during the first week of jaundice. This suggests that the swollen condition of the liver may indicate a greater degree of functional impairment in regard to the excretion of bilirubin.

While all the reactions in this series of cases were of the direct type, Schiff and Eliasberg,⁵¹ in studying a group of thirty cases occurring in

51 Schiff, E, and Eliasberg, H. *Klin Wchnschr* **38** 1891, 1922

50 Jones, C M, and Minot, G R. *Boston M & S J* **189** 531, 1923

children during the winter of 1921 and 1922, found that between October, 1921, and January, 1922, all the serums gave the delayed direct reaction only, whereas a prompt direct reaction was obtained in all subsequent cases, without the least apparent change in the clinical picture

11 *Stone Obstructing the Common Duct*—Four cases of stone obstructing the common duct were studied (table 15). In three, there was a marked "direct" increase in the serum bilirubin, while in the fourth, one of Charcot's intermittent hepatic fever, a transient slight increase during the attacks of pain and chills occurred. In this patient, the relation of bilirubinemia to temperature, chills, pain and number of leukocytes is noteworthy and is given in table 16.

TABLE 15—*Stone Obstructing Common Duct*

No	Age	Sex	Pathologic Diagnosis	Clinical Jaundice	Red Blood Cells	Hemo- globin, per Cent	Mg Bilirubin Direct
1	72	♂	+	+	4,700,000	80	15.0
2	45	♂	+	5 weeks	4,400,000	75	9.4
3	36	♀	—	7 weeks		85	26.0
4	43	♀	+	—		75	1.8

TABLE 16—*Charcot's Intermittent Hepatic Fever (Case 4)*

Time	Temperature	Leukocytes	Pain	Chill	Mg Bilirubin	
					Direct	Indirect
1/3/27 4 00 p m	98.4	9,400	0	0	—	0.6
1/5/27 7 00 p m	103.2	17,800	+	+	1.8	
1/6/27 5 30 p m	99.4	9,000	0	0	—	0.4

Walters⁵² has noted the frequency of stone in the common duct without jaundice. More remarkable is the fact that a stone may be present without even a distinct increase in the serum bilirubin, as in case 4 of this series (between attacks) and in one of eighteen cases of chronic cholecystitis studied.

12 *Tumor Obstructing the Common Bile Duct*—Of particular interest in this series are three instances of a fall in serum bilirubin when a tumor obstructed the common bile duct (table 17). In two, a pathologic diagnosis of carcinoma of the pancreas was made, while in the third a firm tumor of the papilla of Vater, measuring 2 by 5 cm., and thought to be malignant, was encountered at operation. Word was received later from this patient's physician that the jaundice had completely disappeared.

It is of interest to note in case 4 a decline in the hemoglobin and red cell count accompanying the drop in the serum bilirubin, suggesting

⁵² Walters, Waltman. Surg. Gynec. Obst. 42:453, 1926.

a possible cause for the latter. This is in accord with the experiments of Rous and Drury⁵³ in ligation of the common duct, which Poer and I⁵⁴ have had occasion to verify in a number of animals. The appearance of the skin on May 7 was one of mixed green and black jaundice, replacing the yellow tint noted February 4, and yet the bilirubinemia was at its lowest level. This, of course, is only another argument for the importance of the estimation of serum bilirubin. McNee¹⁰ mentions a similar experience.

In case 5, it was surprising to note a serum bilirubin value of only 4 mg (determinations on three successive days), with a jaundice of a month's duration. The tumor may have been of an inflammatory nature. It is unfortunate that autopsy was not obtained in this case.

TABLE 17—*Tumor Obstructing Common Duct*

No	Age	Diagnosis	Duration of Jaundice	Died	Red Blood Cells	Hemoglobin, per Cent	Mg Bilirubin Direct
1*	72	Operative	?	+	4,800,000	65	9.3 (Sept. 3) 13.8 (Sept. 9)
2*	66	Pathologic	5 weeks	+		60	20.0
3*	67	Pathologic	2 weeks	—	5,100,000	74	15.0 (Feb. 4) 17.7 (Feb. 14) 5.0 (May 9)
4*	51	Operative	4 weeks	+	3,400,000 4,900,000	50 70	4.0 (Aug. 31) 4.0 (Sept. 2)
5*	88	Clinical	?	+	5,000,000	70	9.4
6†	59	Operative	?	—			7.5 (Oct. 5) 12.5 (Oct. 16) 9.1 (Oct. 30) 6.3 (Nov. 10)

* Tumor of head of pancreas.

† Exploratory laparotomy showed a firm mass, 2 by 5 cm., at papilla of Vater, with dilatation of common duct. The jaundice eventually disappeared.

SUMMARY

The original observation of Hijmans van den Bergh that increase of serum bilirubin during obstructive jaundice gives a "direct" reaction with Ehrlich's diazo reagent and that increase in hemolytic types of jaundice gives only an indirect reaction has been confirmed.

One milligram per hundred cubic centimeters of serum may be safely considered the upper limit of normal with values between 0.6 and 1 mg. as possibly indicative of increase. The values are somewhat higher among males than females. Values above 1 mg. are encountered in new-born infants.

Estimations of serum bilirubin are of prognostic value in congestive heart failure levels exceeding 1 mg. per cent being frequently followed by fatal termination. Hepatic enlargement does not necessarily signify hyperbilirubinemia.

53 Rous, Peyton, and Drury, D. R. *J. Exper. Med.* **41**: 601, 1925.

54 Poer, H. D., and Schiff, Leon. Unpublished data.

Low values of serum bilirubin were noted in acute alcoholism. Whether this is due to stimulation of excretion of bilirubin is not known.

No increase in the serum bilirubin occurs during the gastric crises of tabes dorsalis, in contrast to attacks of acute gallstone colic.

The constant association of right-sided lesions in lobar pneumonia with the incidence of jaundice in 21 of 826 cases suggests an anatomic factor as possibly operative in the production of hepatitis with jaundice in this disease.

In chronic (splenomegalic) hemolytic jaundice, there may not be any definite relationship between the degree of bilirubinemia and the erythrocytic fragility at a given time. There is evidence substantiating the observation of van den Bergh that certain instances of physiologic hyperbilirubinemia may show some of the characteristics of hemolytic jaundice.

In sickle cell anemia as in chronic hemolytic jaundice (and also pernicious anemia), the serum bilirubin shows an increase of the "indirect" type of van den Bergh.

In hereditary hemorrhagic telangiectasia, relatively low values in serum bilirubin are obtained, as in ordinary secondary anemias.

In acute catarrhal jaundice, there is a tendency for the highest serum bilirubin levels to occur in cases showing demonstrable hepatic enlargement, suggesting in the latter instance a greater degree of functional impairment of the liver.

There is evidence suggesting that the level of the serum bilirubin and the occurrence of jaundice in cases of hepatic malignant disease and cirrhosis may depend on the amount of hemoglobin and the number of red cells circulating in the blood.

The level of serum bilirubin may drop and the jaundice may diminish in the presence of obstruction of the common bile duct by tumor and also in carcinoma of the liver. A simultaneous drop in the hemoglobin and number of red blood cells has been noted in some cases.

DIETARY FACTORS THAT INFLUENCE THE DEXTROSE TOLERANCE TEST

A PRELIMINARY STUDY *

J SHIRLEY SWEENEY, M D

DALLAS, TEX

The dextrose tolerance test is now being extensively employed as a diagnostic procedure. It is most beneficially used in the differentiation of mild diabetes mellitus and renal diabetes. It is also being used, and is believed to be of diagnostic value, in many pathologic conditions, such as encephalitis, malignant tumor, pituitary and thyroid dysfunctions and nephritis ¹

Although it is definitely established as a diagnostic procedure, there is some diversity of opinion concerning what constitutes a normal response to the oral administration of dextrose. Some writers state that in a healthy person there may be a postprandial rise in blood sugar of from 14 to 16 per cent and a return to the normal within two hours ². There are other writers ³ who consider a postprandial hyperglycemia of 20 per cent within normal limits. It is generally believed that the persistence of the postprandial hyperglycemia is of more diagnostic significance than the degree of hyperglycemia ⁴. In early cases of diabetes the blood sugar curve rises higher, stays up for a longer time and does not return to normal for several hours. Macleod says that "slight deviations from the normal must not be given too much weight in diagnosis, since they may occur in other diseases or even in perfectly normal persons" ⁵.

All who have studied dextrose tolerance curves have noted the variability exhibited by normal persons, to say nothing of those who are

* From the Departments of Internal Medicine and Physiology, Baylor University, College of Medicine

1 Gray, Horace. Blood Sugar Standards in Conditions Neither Normal nor Diabetic, *Arch Int Med* **31** 259 (Feb) 1923. John, H. J. *Ann Clin Med* **5** 340, 1926. Friedenwald, J., and Grove, J. G. *Am J M Sc* **33** 163, 1922. Paullin, J. E., and Sauls, H. C. *South M J* **15** 249, 1922. Mosenthal, Herman O. *M Clin N Amer* **9** 549, 1925.

2 Mosenthal (footnote 1, fifth reference). Macleod. *Physiology and Biochemistry in Modern Medicine*, ed 5, St. Louis, C. V. Mosby Company, 1926, p. 876.

3 Hale-White, R., and Payne, W. W. *Quart J Med* **19** 393, 1926. Gilbert, Max, Schneider, Hans, and Bock, Joseph C. *J Biol Chem* **68** 629, 1926.

4 Mosenthal (footnote 1, fifth reference). John, H. J. *J M Research* **4** 255, 1923.

5 Macleod (footnote 2, second reference).

diseased These variations have been discussed and explained in different ways ⁶

It occurred to me that perhaps the character of the food and the amount of water that a person had been consuming for a few days prior to the time the tolerance test was made might be factors that would influence the dextrose tolerance curve If these factors should prove to be capable of altering a tolerance curve, they could be controlled This would eliminate some of the confusing variability that is so frequently observed It was these thoughts that lead to the following experiments

Young, healthy, male medical students were used to study the effect of different preceding diets Four groups were formed The subjects in one group were given a protein diet, those in another a fat diet, those in a third a rich carbohydrate diet, and those in the fourth group were not given any food—the starvation group Those on the protein diet received only lean meat and the whites of eggs The students on the fat diet received only olive oil, butter, mayonnaise made with egg yolk, and 20 per cent cream Those in the group fed on carbohydrates were allowed sugar, candy, pastry, white bread, baked potatoes, syrup, bananas, rice and oatmeal These diets were followed for two days Meals were taken at the usual hours, and eating between meals was allowed, provided the diets were followed Those in the starvation group did without food for two days On the morning of the third day, each student was given by mouth 1.75 Gm of dextrose per kilogram of body weight, on an empty stomach Determinations of blood sugar were made from samples of venous blood removed immediately before the dextrose was given, and at 30, 60 and 120 minute intervals following its administration I made all determinations of blood sugar by the Folin-Wu method ⁷

The results of these tests are listed in tables 1, 2, 3 and 4, and in charts 1, 2, 3 and 4 It will be noted that the curves are strikingly different The persons who starved and those who were placed on the fat diet present the most abnormal responses to the administration of dextrose In no instance did the blood sugar return to normal within two hours The most atypical curve of these two groups is that of subject W, whose blood sugar rose to 0.286 mg per hundred cubic centimeters of blood at the two hour observation This student was nauseated, which probably explains not only the delayed rise, but also

⁶ Mosenthal (footnote 1, fifth reference) McCaskey, G W The Basal Metabolism and Hyperglycemic Tests of Hyperthyroidism, *J A M A* **73**:243 (July 26) 1919 Rohdenburg, G L, Bernhard, A, and Krebbiel, O *Am J M S* **159** 577, 1920

⁷ Folin and Wu *J Biol Chem* **38** 81, 1919

TABLE 1—Results of Dextrose Tolerance Tests on Four Normal Young Adults (Medical Students) Who Had Been Eating Only Proteins for Two Days Prior to Tests

Subject	Age	Dextrose Gm	Fasting	Blood Sugar Mg per 100 Cc		
				After Dextrose		
				30 Minutes	60 Minutes	120 Minutes
S	23	95	69	143	148	154
T	25	140	75	148	182	
C	25	110	62	125	168	155
Mc	25	136	71	155	172	125

TABLE 2—Results of Dextrose Tolerance Tests on Five Normal Young Adults Who Had Been Placed on the Fat Diet for Two Days Prior to the Tests

Subject	Age	Dextrose Gm	Fasting	Blood Sugar Mg per 100 Cc		
				After Dextrose		
				30 Minutes	60 Minutes	120 Minutes
W	26	71	69	100	95	286
B	25	137	78	143	178	133
S	23	119	80	170	232	190
B2	21	105	95	222	219	170
J	22	119	80	143	195	200

TABLE 3—Results of Dextrose Tolerance Tests on Eight Normal Young Adults Who Had Been Placed on the Carbohydrate Diet for Two Days Prior to Tests

Subject	Age	Dextrose Gm	Fasting	Blood Sugar Mg per 100 Cc		
				After Dextrose		
				30 Minutes	60 Minutes	120 Minutes
C	23	85	74	111	125	111
N	25	115	78	111	101	88
J	24	126	75	85	97	85
A	22	141	80	148	111	85
F	25	125	80	121	143	105
Jack	24	165	98	148	108	100
J2	22	119	82	121	114	82
S	23	119	89	111	73	83

TABLE 4—Results of Dextrose Tolerance Tests of Five Normal Young Adults Who Starved for Forty-Eight Hours, Only Water Being Taken

Subject	Age	Dextrose Gm	Fasting	Blood Sugar Mg per 100 Cc		
				After Dextrose		
				30 Minutes	60 Minutes	120 Minutes
J	24	124	71	133	167	235
A	22	145	61	143	182	229
M	25	143	58	114	160	129
D	25	149	67	113	178	131
R	21	139	72	157	242	174
C	23	119	74	211	200	205

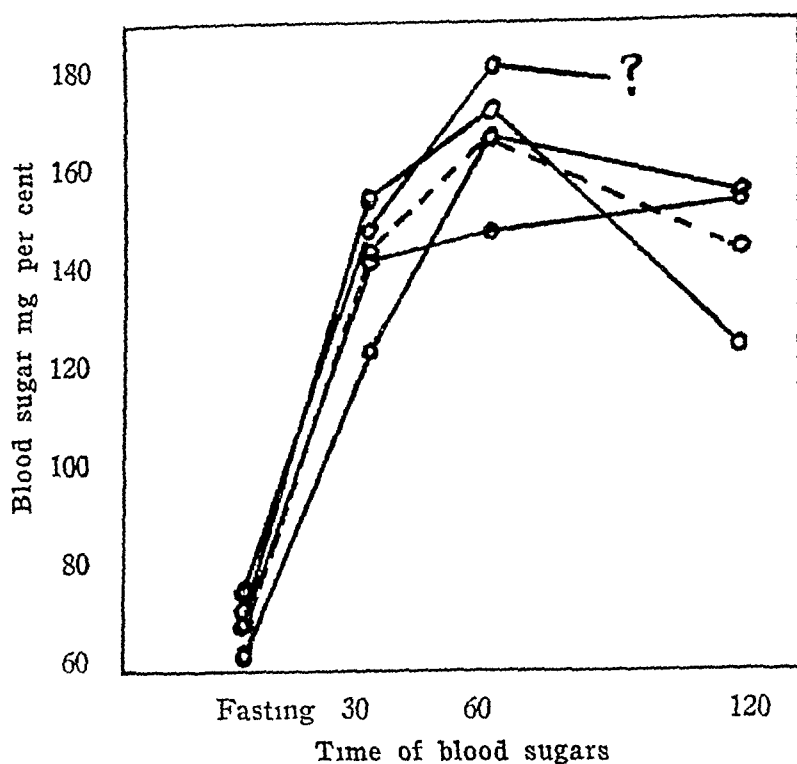


Chart 1—Graph showing dextrose tolerance curves of four normal young adults who had been eating a protein diet for two days The dash line in all charts is the average or type curve

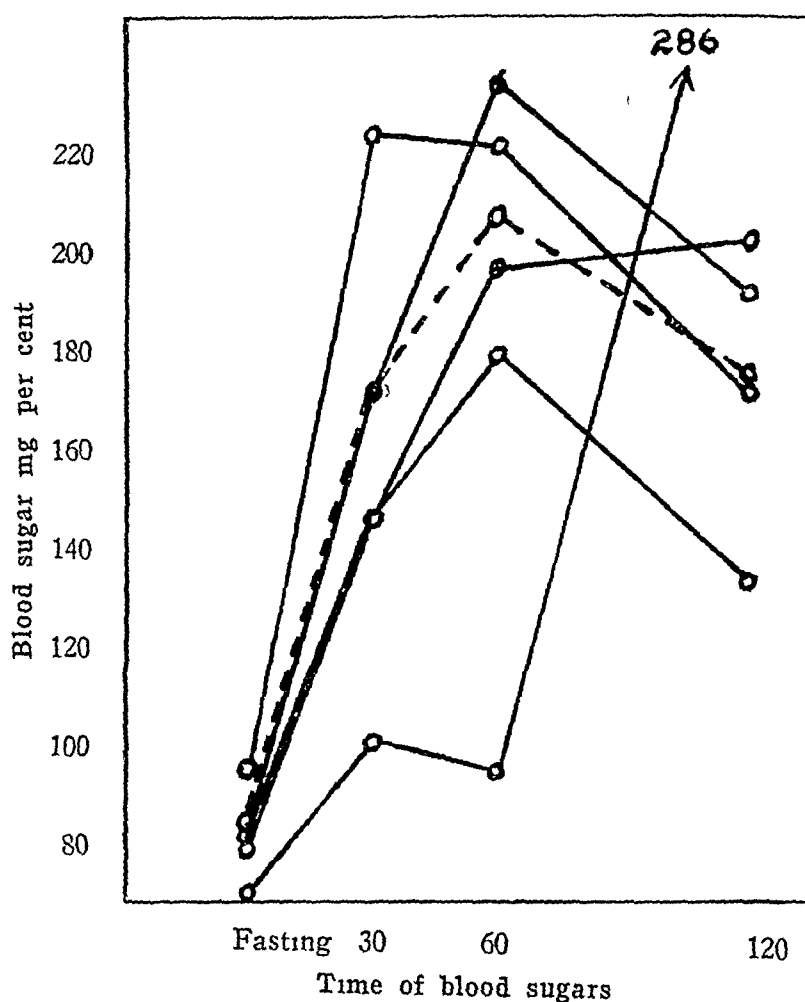


Chart 2—Graph showing dextrose tolerance curves of five normal young adults who had been eating a fat diet for two days

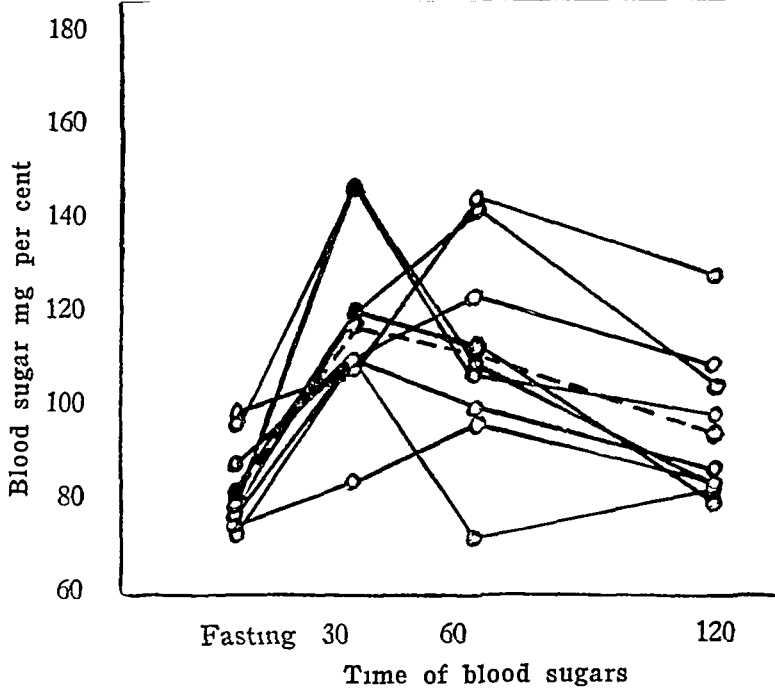


Chart 3—Graph showing dextrose tolerance curves of nine normal young adults who had been eating a rich carbohydrate diet for two days

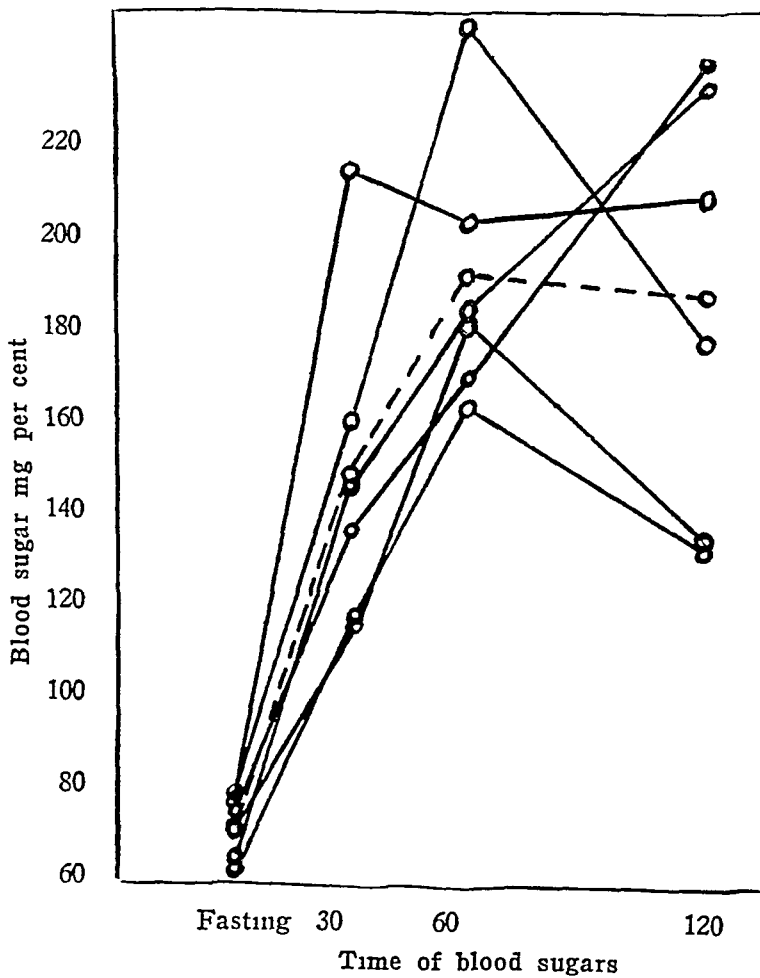


Chart 4—Graph showing dextrose tolerance curves of six normal young adults who did without food for two days, taking only water

the slight drop at the one hour observation. This effect of nausea has been pointed out previously.⁸

The groups fed on protein and on carbohydrates, especially the latter, showed a marked contrast to the other groups. Judged by some standards, none of the curves for the protein group should be considered normal. Those in the carbohydrate group are all strikingly within normal limits, in fact, the highest postprandial rise in this group was to a level of 0.148 mg per hundred cubic centimeters of blood. The highest two hour observation was to 0.111mg.

A better comparison of these groups is obtained by examining table 5 and chart 5 in which are contained the average or type curves of each group. It will be noted that those students who were on the carbohydrate diet exhibited a marked increase in sugar tolerance and those on a protein diet a slight decrease in tolerance, while those who were placed on the fat diet and those who were starved manifested a definite

TABLE 5—Table Showing Average Dextrose Tolerance Curves or Type Curves of the Students in the Four Different Dietary Groups

Diet Groups	Blood Sugar Mg per 100 Cc			
	Fasting	After Dextrose		
		30 Minutes	60 Minutes	120 Minutes
Fats *	83	170	206	173
Protein	69	143	167	145
Carbohydrate	84	118	113	96
Starvation	67	145	188	184

* Averages excluding curve of subject W, who was nauseated

decrease in sugar tolerance. The differences in the average fasting blood sugars are noteworthy. The blood sugar in those of the protein and starvation groups was distinctly lower than that of the members of the fat and carbohydrate groups.

Because of the great difference in these groups, those students on the fat diet and those in the starvation group who showed the most extreme responses were placed on the carbohydrate diet. Similarly, those in the carbohydrate group who showed an extreme response were placed on starvation restriction. This was obviously done to determine whether the curve of a person could be changed significantly by diet. The results are presented in table 6 and in charts 6 and 7.

Comparison of the curves of these five students is striking. The curves of all who had been placed on carbohydrate diets manifested a definite increase in their sugar tolerance. When three of these (the three most extreme) were placed on starvation restrictions, the curves were notably abnormal, there was a marked postprandial hyperglycemia,

8 Hale-White and Payne (footnote 3, first reference)

which persisted at the end of two hours, in other words, what was an increased sugar tolerance following the carbohydrate diet became a definitely decreased tolerance following two days of starvation. The remaining two persons who were placed on the fat diet showed a similar decreased tolerance. It should be stated that an interval of at least one week was allowed between the tolerance tests performed on the same subject.

It is plain from the foregoing experiments that the dextrose tolerance test may be significantly affected by the character of food taken prior to

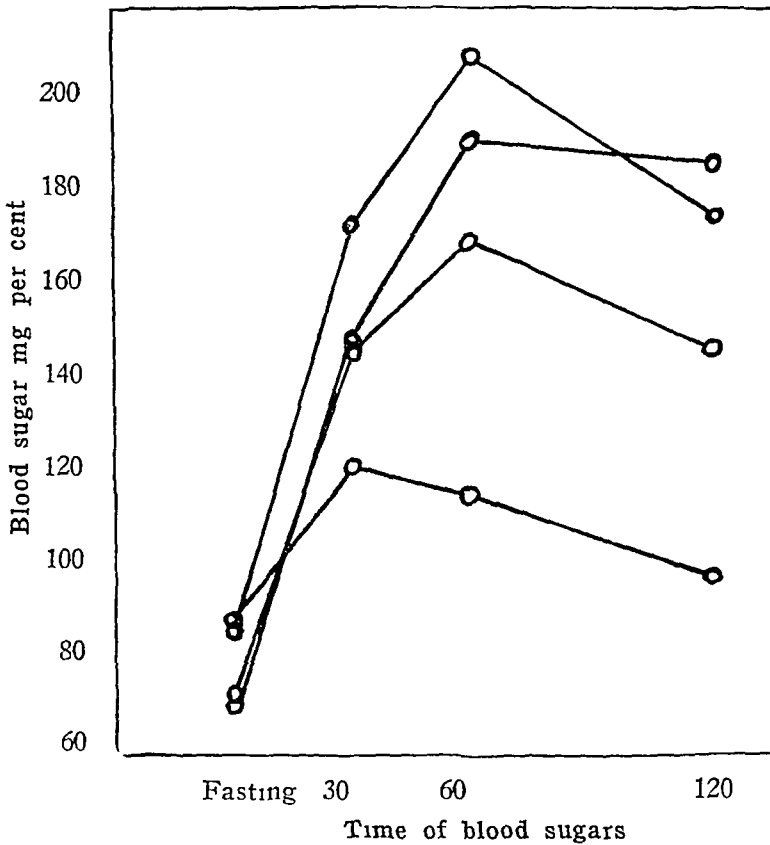


Chart 5—Graph showing the average or type curves (figures in table 5) Reading from below upward on the two hour ordinate, the curves are as follows first, carbohydrate, second, protein, third, fat, and fourth, starvation

the test. Practically, this means that a standardized diet should be worked out to be followed prior to the performance of the dextrose tolerance test. It is reasonable to believe that if a dextrose tolerance curve can be so materially altered by two days of such restriction of the diet as has been shown, that a standardized diet would have the tendency to cause a less variable response. In this connection it is possible that some of the atypical curves that have been noted in different pathologic conditions may in reality be due to the diets indicated and

taken in such states Likewise, some of the slightly abnormal curves noted in healthy persons may have the same basis of explanation

Dogs were used for the purpose of studying the effect of hydration and dehydration on dextrose tolerance To dehydrate the animal, all water was withheld for two days To increase the body fluids, 500 cc of physiologic sodium chloride was injected intraperitoneally on the day preceding the test, and 350 cc more was injected two hours before

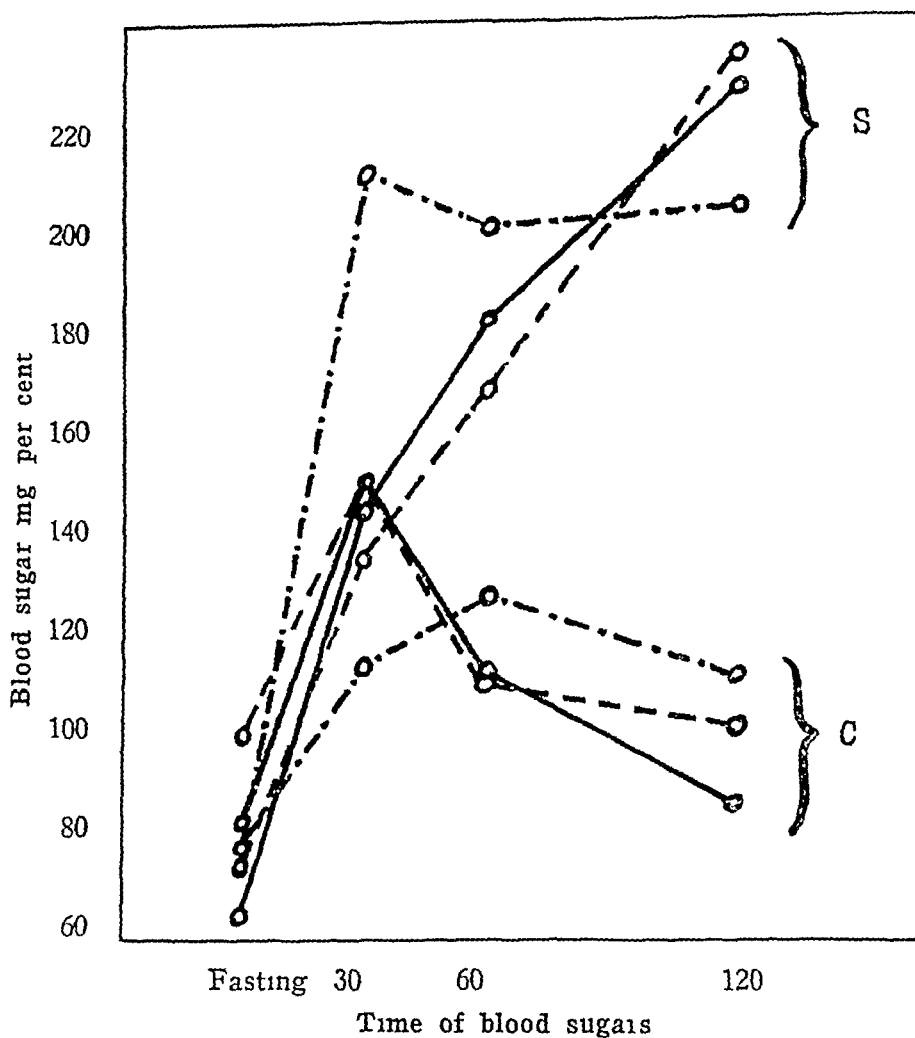


Chart 6—Graph showing two curves for each of three normal young adults In one instance—the curves marked S—the students were starved for two days prior to the test, in the other instance—the curves marked C—they were fed the carbohydrate diet Similar lines represent the same subjects

the dextrose was administered⁹ All dogs were given 2 Gm of dextrose per kilogram of body weight by stomach tube The dextrose was diluted with water to make a 20 per cent solution Samples of blood were drawn as already described for medical students All determinations were made by M¹ R W Lackey of the physiology department The

⁹ Andrews, Edmund Water Metabolism, Sugar Metabolism in Dehydration, Arch Int Med **38** 136 (July) 1926

Hartmann-Shaffer method was used¹⁰ All dogs received a mixed diet containing varying proportions of meat, bread and vegetables

In tables 7 and 8 are listed the results obtained on five hydrated and two dehydrated dogs, respectively The same results are presented graphically in charts 8 and 9 The dash line in each chart is the average

TABLE 6—*Table Showing the Dextrose Tolerance Figures of Five Medical Students, Each of Whom Was Placed on Two Different Diet Restrictions, as Indicated for Two Days Prior to the Tests An Interval of at Least One Week Was Allowed Between Tests on the Same Individual*

Subject	Age	Diet	Dextrose Gm	Blood Sugar Mg per 100 Cc			
				Fasting	After Dextrose		
					30 Minutes	60 Minutes	120 Minutes
A	22	Starvation	145	61	143	182	229
		Carbohydrate	141	80	148	111	85
Jack *	24	Starvation	124	71	133	167	235
		Carbohydrate	165	98	148	108	100
C *	23	Starvation	119	74	211	200	205
		Carbohydrate	85	74	111	125	111
J	22	Fat	119	80	143	195	200
		Carbohydrate	119	82	121	114	82
S	23	Fat	119	80	170	232	190
		Carbohydrate	119	89	111	73	83

* It will be seen that the amounts of dextrose given to students Jack and C differed for the two tests This was due to an error in the arithmetic It is noteworthy that these errors varied in such a way as to make the effect inconsequential

TABLE 7—*Results of Dextrose Tolerance Test on Five Dogs That Had Received 850 cc Physiologic Sodium Chloride Intraperitoneally Prior to the Test*

Subject	Dextrose Gm	Blood Sugar Mg per 100 Cc			
		Fasting	After Dextrose		
			30 Minutes	60 Minutes	120 Minutes
Dog 1	20	115	112	171	166
Dog 2	20	100	118	126	113
Dog 3	20	113	125	132	156
Dog 4	28	93	107	134	133
Dog 5	30	100	150	149	140

TABLE 8—*Results of Dextrose Tolerance Test on Two Dogs That Had Not Received Any Water for Two Days Prior to the Test*

Subject	Dextrose Gm	Blood Sugar Mg per 100 Cc			
		Fasting	After Dextrose		
			30 Minutes	60 Minutes	120 Minutes
Dog 1	25	87	169	201	113
Dog 2	32	90	139	162	148

curve Three interesting differences are noted in the comparison of these two groups First, there seems to be a lower blood sugar in the dehydrated animals while fasting, second, the postprandial hyperglycemia is distinctly less at the thirty minute observation in the hydrated

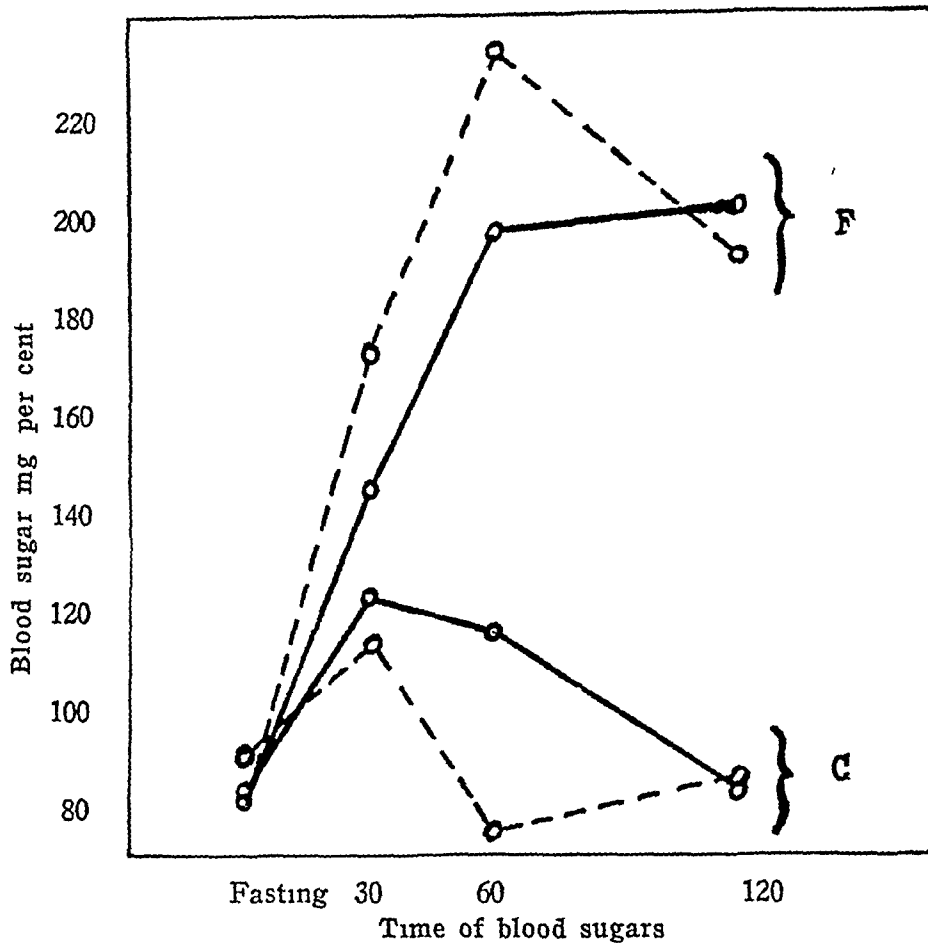


Chart 7—Graph showing two curves each of two normal young adults. In one instance—the curves marked *F*—the students were fed the fat diet for two days prior to the test, in the other instance—the curves marked *C*—they were fed the carbohydrate diet. Similar lines represent the same subjects.

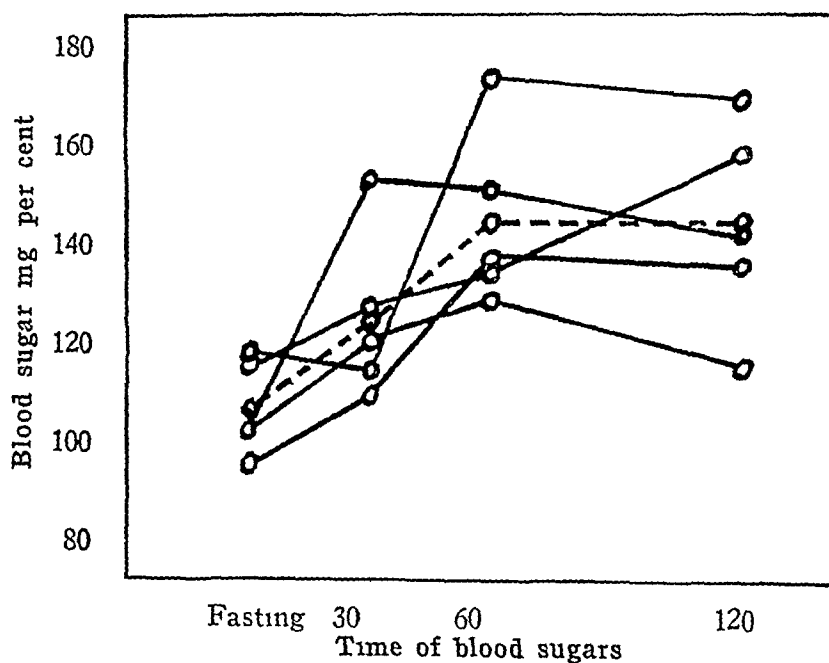


Chart 8—Graph showing sugar tolerance curves of five hydrated dogs. These animals received 850 cc of physiologic sodium chloride intraperitoneally.

dogs, and third, there seems to be a tendency toward a delayed return to normal at the two hour period in the hydrated animals. It will be noted that one hydrated dog (dog 5, table 7) showed a marked thirty minute rise in blood sugar as compared to the others in this group. This animal was extremely nervous. Every time he was handled he would become rigid and remain so until placed back in his cage. The factors involved in this phenomenon may explain the comparatively abrupt thirty minute rise in blood sugar.

It is unwise to conclude much from so few observations. It is believed, however, that the really significant result of this experiment is

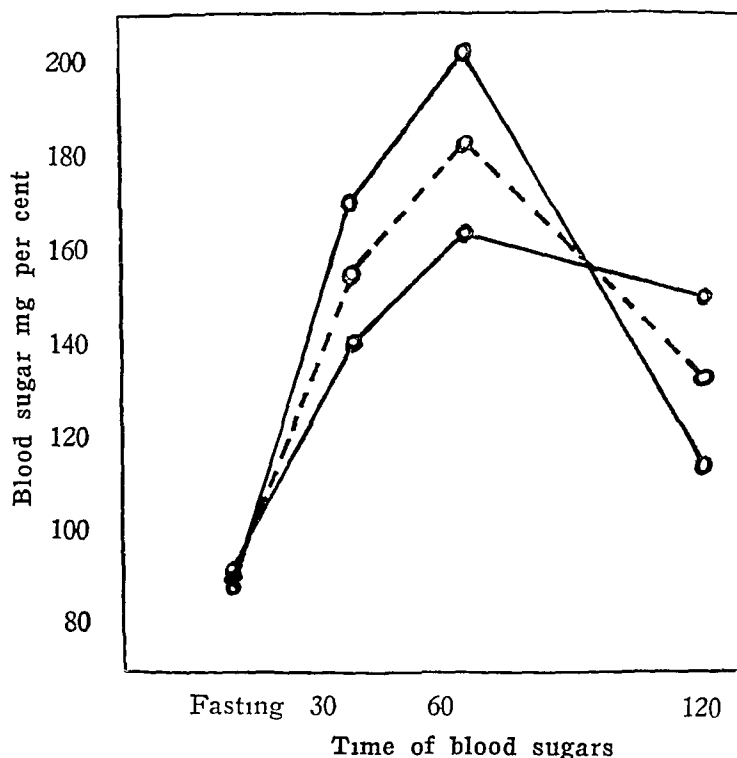


Chart 9—Graph showing dextrose tolerance curves of two dehydrated dogs. All fluids were withheld for two days.

the delayed initial rise of blood sugar in the hydrated animals. This result is most probably explained on the basis that a mild transient hydremia was produced by intraperitoneal injections of physiologic sodium chloride. More experiments are being performed on hydrated and on dehydrated animals in which the diets are standardized.

COMMENT

It may be stated with reasonable accuracy that the major portion of the dextrose ingested during a dextrose tolerance test is converted into glycogen. The height of the postprandial hyperglycemia, the rapidity of the rise and the persistency of the hyperglycemia may be said to be

dependent on the degree of activity of this glycogenic function. Recent experimental evidence has been accumulated which tends to ascribe a strictly anabolic function to insulin.⁵ Lawrence¹¹ has recently presented good experimental evidence favoring the anabolic function of insulin. By this conception, that is, that insulin has principally a glycogenic function, one may readily explain the behavior of the dextrose tolerance curves obtained not only in the subjects in this study, but also in healthy persons and in patients with diabetes mellitus. One assumption, however, is necessary, namely, that the ingestion of carbohydrates activates an intermediate hormone which in turn stimulates the production of insulin. This is certainly reasonable from a physiologic point of view.

With these points in mind it may be said, in explanation of the normal dextrose tolerance curve, that when dextrose is taken, a hormone is produced which stimulates the production of insulin. The result is only a moderate postprandial rise in blood sugar until the insulin that has been produced has caused active glycogenesis.¹²

In health and as a result of daily eating of the usual mixed diet, this mechanism is working smoothly and flexibly, in other words, the response to carbohydrate ingestion is normal. In case of diabetes, although the hormonal response is normal after the ingestion of dextrose, the amount of insulin that is produced is insufficient to store the dextrose as glycogen, and there is a resultant hyperglycemia and a prolonged curve.

In the curves of the subjects fed on carbohydrate there is an insignificant rise in the blood sugar. This phenomenon, therefore, may be explained by the more active functioning of the hormone stimulating process as a result of an excessive intake of carbohydrates. Consequently, when dextrose was administered, there was no delay in this mechanism, and the stimulation with insulin was more prompt, the result was quick and active glycogenesis.

In those persons who were on protein diets only a slight variation from the normal was found in their response to dextrose. This may possibly be explained on the basis of the carbohydrate content of protein.

In the next group of patients, namely, those receiving fats, the curves fall just where one would expect them to according to the theory proposed. As a result of much ingestion of fat, the activation of the insulin stimulating hormone has been reduced. This would cause a sluggish response when dextrose is ingested, therefore, a rather steep rise in the blood sugar occurs until the insulin stimulating process has been completed.

¹¹ Lawrence, R. D. *Quart J Med* **20** 69 (Oct) 1926.

¹² This term is used rather loosely. I am aware of other probable actions of insulin (reference 5).

What has been said of the curves for the subjects on the fat diet may be said for those of the subjects in the starvation group. It is interesting to note that the average curve for the subjects fed on fats showed evidence of a slightly quicker response, that is, a reduction in blood sugar, than did the average curve for the starvation group. This may possibly be due to the small percentage of carbohydrate that fat yields.

Joslin, as well as others, for a long time has stressed the overeating of starches and sugars as important etiologically in diabetes mellitus. The foregoing results tend to strengthen this belief. Whatever lies behind the innate desire for sweets, overeating of them by some persons may impair an inherently weakened insulin producing organ. As a result, when glycogenesis is lessened, the storage of fat increases and the weight increases, an almost invariable fact in the anamnesis of any diabetic person. Diabetes mellitus follows varying periods of obesity.

CONCLUSIONS

1 The dextrose tolerance test, as usually employed, has been shown to be materially influenced by different antecedent foods or diets, and to some degree by the preliminary intake of water. It is suggested that a standardized antecedent diet might eliminate the variability produced by different foods. It is further suggested that some of the dextrose tolerance curves believed to be peculiar to different pathologic conditions might result from the diets indicated or taken in such conditions.

2 The principal effect of hydration or dehydration on the dextrose tolerance curve appears to be a delayed thirty minute postprandial rise in blood sugar in hydrated animals. This was interpreted on the basis of a transient hydremia.

3 Dextrose tolerance tests performed on medical students are shown to vary definitely with the character of the antecedent diet. Four different types of curves are presented—the protein, fat, carbohydrate and starvation curves. These curves are distinctly different and are obtained by simply restricting the diet to protein, fat, carbohydrate and starvation for two days prior to the test.

CHEMICAL STUDIES IN TUBERCULOSIS

I PLASMA PROTEINS, CHOLESTEROL AND CORPUSCLE VOLUME *

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Medical literature reveals extensive work on cholesterol and plasma protein content of the blood in health and in various diseases, but only a limited number of the reports contain data on pulmonary tuberculosis. Since the onset and the course of development of tuberculosis are comparatively slow, the changes in the blood are likewise slow, in striking contrast to the rapid changes found in pneumonia. As a result of this gradual change, various stages of tuberculosis present chemical pictures as opposite as those found in different diseases. Therefore, to formulate definite conclusions regarding chemical changes in the blood, repeated examinations supplemented with clinical observation should be made on subjects representing all stages of tuberculosis.

The purpose of this work is to ascertain a possible relationship of the plasma proteins, cholesterol and corpuscle volume to the different stages of tuberculosis. Single determinations were made on seventy-one patients, and repeated determinations on thirty-eight.

METHODS

The blood was drawn before breakfast from the antecubital vein in a Keidel tube containing 2 mg of neutral potassium oxalate per cubic centimeter of blood. The cholesterol was determined in the whole blood, and the proteins were determined in the plasma. For analyses the standard methods for plasma proteins,¹ cholesterol² and cell volume³ were employed. Analyses were made in duplicate, and satisfactory checks were obtained in all results reported. The results are given in table 1.

COMMENT

The corpuscle volume depends on two factors: the number and the size of the erythrocytes. A low erythrocyte value in tuberculosis is always accompanied by a low corpuscle volume, but a low corpuscle volume is not always accompanied by a low erythrocyte count. In fact,

¹ From the Research Laboratories, Chemical Department, of the City of Chicago Municipal Tuberculosis Sanitarium.

¹ Wu. The Determination of Plasma Proteins, *J Biol Chem* **51** 33 (March) 1922.

² Bloor. Determination of Cholesterol in Blood, *J Biol Chem* **24** 227 (Feb) 1916.

³ Sundstroem and Bloor. The Physiological Effects of Short Exposures to Low Pressures, *J Biol Chem* **45** 153 (Dec) 1920-1921.

the red cell count may be normal or even higher. This decrease in the corpuscle volume is due to a shrinkage in the size of the cell, a phenomenon which perhaps can be attributed to a disturbance in the osmotic pressure of the body fluids. The determination in the individual cell volume appears to depend on a loss in the water content rather than on the other constituents. As evidence, the phosphorus⁴ content of the individual red cell in tuberculosis, although decreased in size, was found to be equal to or greater than that of the normal cell.

A definite disturbance in cholesterol metabolism occurs in tuberculosis. The cholesterol content of the blood may be either hyponormal or hypernormal. The increase may be attributed to one or more of the following factors:

The first is the immunization against infection. The relationship between cholesterol and immunity is probably due to the action of cholesterol against toxins as exhibited by the fact that hemolysis by saponin is prevented by cholesterol. The second is the need for

TABLE 1—Average Normal Values

	Percentage	Percentage
Corpuscle volume	45 (Men)	40 (Women)
Fibrin	0.300	± 0.05
Albumin	4.900	± 0.3
Globulin	2.200	± 0.4
Albumin plus globulin	7.100	
Albumin / Globulin } ratio, 2.2		
Cholesterol, 185 mg per 100 cc		

replenishing new cells lost through destruction of tissue, since cholesterol is a necessary constituent of all cells. The third factor is the destruction of cells, which liberates the cholesterol.⁵ It is not excreted as a waste product, but is utilized for the formation of new cells.

A similar disturbance is expected in all tissues, associated with the disturbance in the blood cholesterol. Chauffard⁶ found a definite equilibrium between the cholesterol content of the blood and the suprarenals in various diseases. The disturbance of the cholesterol in the tissues would modify the water content, since it has been shown that tissues with the most cholesterol have the greatest power of imbibing and holding water. Thus great emaciation and dehydration of body tissue (far advanced phthisis) should show a hypocholesterolemia. This condition suggests a diet of food rich in cholesterol, such as eggs and

4 McCluskey. The Distribution of Phosphorus Compounds in the Blood in Tuberculosis, *J Lab & Clin Med* **10** 466 (March) 1925.

5 Dorée and Gardner. *Proc Roy Soc, London, B*, **81** 109, 1908.

6 Chauffard, quoted by Shafer, E. Sharpley. *Endocrine Organs*, London, 1924, p 109.

Tuberculosis

men with Pulmonary

... on Blood in Women
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TABLE 2—Observations on Tuberculosis Association Classifications												
Case	Date	Age	Cor-puscle Volume, Per-centage	Leuko-cytes 10 ⁶	Hemo-globin, gwtst Test	Per-cent age of Albu-min	Per-cent age of Glob-ulin	Total age of Serum Albumin to Globulins	Ratio of Albumin to Globulin	Choles-terol Mg per 100 Cc	Asso-ciation Classification*	Comment
1	12/6/26	30	10.6	157	70	1.508	2.618	7.126	1.722	169.5	F A C	Sputum positive, Wassermann negative, died 2/19/27
2	3/11/26	30	31.1	184	0.182	1.508	2.618	7.126	1.722	169.5	F A C	Sputum positive, Wassermann negative, died 7/20/26
3	12/13/26	18	29.5	10	0.636	3.525	2.930	7.150	1.553	121.6	F A B	Sputum positive, Wassermann negative, hemorrhage of Pott's disease
4	12/13/26	18	31.9	131	0.569	4.382	3.001	7.433	1.478	101.1	F A B	Sputum positive, Wassermann negative, discharged
5	6/29/26	20	30.8	472	0.533	1.135	1.238	8.166	0.911	101.1	F A B	Sputum positive, Wassermann negative, fluid in chest
6	10/1/26	17	33.1	50	0.513	3.938	1.238	8.166	0.911	101.1	F A B	Sputum positive, Wassermann negative, died 8/25/26
7	9/23/26	21	30.7	40	0.473	1.352	2.707	7.089	1.619	161.8	F A B	Sputum positive, Wassermann negative
8	9/23/26	21	30.7	40	0.637	4.720	2.810	7.175	1.556	167.6	F A B	Sputum positive, Wassermann negative
9	7/29/26	27	39.0	128	0.413	1.183	1.163	8.316	1.028	168.1	F A B	Sputum positive, Wassermann negative
10	7/29/26	21	31.3	111	0.680	2.689	6.676	9.365	0.103	175.8	F A B	Sputum positive, Wassermann negative
11	8/2/26	22	32.0	163	0.179	5.365	2.797	8.162	1.198	200.9	F A B	Sputum positive, Wassermann negative
12	8/2/26	22	32.0	163	0.179	5.365	2.797	8.162	1.198	200.9	F A B	Sputum positive, Wassermann negative
13	8/2/26	22	32.0	163	0.179	5.365	2.797	8.162	1.198	200.9	F A B	Sputum positive, Wassermann negative
14	8/2/26	22	32.0	163	0.179	5.365	2.797	8.162	1.198	200.9	F A B	Sputum positive, Wassermann negative
15	8/2/26	22	32.0	163	0.179	5.365	2.797	8.162	1.198	200.9	F A B	Sputum positive, Wassermann negative
16	8/2/26	22	32.0	163	0.179	5.365	2.797	8.162	1.198	200.9	F A B	Sputum positive, Wassermann negative
17	8/2/26	22	32.0	163	0.179	5.365	2.797	8.162	1.198	200.9	F A B	Sputum positive, Wassermann negative
18	8/2/26	22	32.0	163	0.179	5.365	2.797	8.162	1.198	200.9	F A B	Sputum positive, Wassermann negative
19	8/2/26	22	32.0	163	0.179	5.365	2.797	8.162	1.198	200.9	F A B	Sputum positive, Wassermann negative
20	8/2/26	22	32.0	163	0.179	5.365	2.797	8.162	1.198	200.9	F A B	Sputum positive, Wassermann negative
21	8/2/26	22	32.0	163	0.179	5.365	2.797	8.162	1.198	200.9	F A B	Sputum positive, Wassermann negative
22	8/2/26	22	32.0	163	0.179	5.365	2.797	8.162	1.198	200.9	F A B	Sputum positive, Wassermann negative
23	8/2/26	22	32.0	163	0.179	5.365	2.797	8.162	1.198	200.9	F A B	Sputum positive, Wassermann negative
Average	7/11/26	26	35.9	35.9	5.62	0.525	5.119	3.588	8.717	138.4	F A A	Sputum positive, Wassermann negative
24	7/11/26	19	46.8	36.3	3.92	0.413	1.783	2.218	7.672	160.6	F A A	Sputum positive, Wassermann negative
25	12/3/26	17	36.3	36.3	1.89	0.413	1.783	2.218	7.672	160.6	F A A	Sputum positive, Wassermann negative
26	10/13/26	31	36.0	36.0	5.64	0.100	1.846	2.819	7.833	153.3	F A A	Sputum positive, Wassermann negative
27	9/16/26	21	36.0	36.0	1.39	0.100	1.846	2.819	7.833	153.3	F A A	Sputum positive, Wassermann negative
28	9/20/26	22	36.0	36.0	1.39	0.100	1.846	2.819	7.833	153.3	F A A	Sputum positive, Wassermann negative
29	9/20/26	23	36.0	36.0	1.39	0.100	1.846	2.819	7.833	153.3	F A A	Sputum positive, Wassermann negative
30	12/16/26	17	36.0	36.0	1.39	0.100	1.846	2.819	7.833	153.3	F A A	Sputum positive, Wassermann negative
Average	12/16/26	18	36.0	36.0	1.39	0.100	1.846	2.819	7.833	153.3	F A A	Sputum positive, Wassermann negative
31	10/28/26	14	36.0	36.0	1.39	0.100	1.846	2.819	7.833	153.3	F A A	Sputum positive, Wassermann negative
32	9/30/26	23	36.0	36.0	1.39	0.100	1.846	2.819	7.833	153.3	F A A	Sputum positive, Wassermann negative
33	9/30/26	23	36.0	36.0	1.39	0.100	1.846	2.819	7.833	153.3	F A A	Sputum positive, Wassermann negative
Average	11/23/26	23	36.0	36.0	1.39	0.100	1.846	2.819	7.833	153.3	F A A	Sputum positive, Wassermann negative

* The National Endowments, 227
divided into three gradations,

TABLE 3—Observations on Blood in Women with Pulmonary Tuberculosis

Case	Date	Age	Cor- puscle Volume, Litho- Per- centage	Leuko- cytes 10 ⁶	Hemo- globin, Tail- qvist Test	Per- cent- age of Albu- min	Per age of Glob- ulin	Total Percent of Serum Pro- teins	Ratio of Albumin to Globulin	National Tuberculosis Asso- ciation Classi- fication	Comment
72	9/30/23 12/13/26	21 30	31.7 40.7	3.83 4.55	8.2 9.85	0.513 0.366	2.707 3.039	7.419 7.972	1.632 1.624	F A B F A B	Sputum positive, Wassermann negative Sputum positive, empyemic fluid Weight 102 pounds (46.8 Kg.), sputum positive, Was- sermann negative
73	5/15/26	30	35.2			0.463	7.207	11.135	0.433	F A B	
	7/26/26		36.0	5.18	13.3	0.497	4.115	8.083	0.965	F A B	Discharged 12/31/26, improved
	12/29/26		38.8	5.46	12.25	0.443	2.583	8.224	2.184	F A A	Sputum positive, Wassermann negative
74	6/17/26	31	34.3	4.84	9.0	0.541	4.703	9.175	0.951	F A B	Discharged 4/14/27, improved
	3/14/27		39.3	5.0	14.9	0.505	3.355	7.555	1.252	F A A	
75	8/20/26	22	28.0	4.41	16.25	0.432	4.780	8.824	0.843	F A B	Sputum positive, Wassermann negative
	4/1/27		31.7	4.76	11.45	0.410	2.610	6.931	1.621	F A A	Sputum negative, clinically improved
76	8/2/26	14	39.4	4.83	12.60	0.517	3.931	8.756	1.227	F A B	Sputum positive, Wassermann negative
	4/1/27		44.7	4.95	13.1	0.331	2.301	7.191	2.125	F A B	Sputum negative, arrested
77	9/16/26	23	33.2	6.22	7.75	0.547	2.714	8.355	2.079	M A B	Sputum positive, Wassermann negative
	3/20/27		40.7	4.51	10.0	0.468	3.201	8.391	1.622	M A A	Sputum negative, discharged 3/20/27, apparently arrested
78	3/25/26	21	39.8	5.0	8.6	0.388	3.875	8.765	1.232	M A B	Sputum positive, Wassermann negative
	2/10/27		46.8	5.1	8.2	0.328	1.713	6.805	2.972	M A B	Discharged 4/14/27, improved, sputum negative
79	6/17/26	28	33.5	4.13	10.6	0.455	4.504	9.049	1.010	M A B	Sputum positive, Wassermann negative, weight 115 pounds (52.1 Kg.)
	12/11/26		44.7	5.13	17.4	0.360	2.353	7.493	2.184	M A A	Weight 118 pounds (53.5 Kg.), sputum negative, dis- charged 12/15/26, improved
80	6/29/23	19	35.8	4.27	13.0	0.258	3.895	8.498	1.182	M A A	Sputum positive, Wassermann negative
	10/13/26		39.4	4.49	12.0	0.368	2.910	7.843	1.695	M A A	Discharged 10/13/26, quiescent
81	8/17/26	15	32.9	4.49	6.7	0.412	3.413	8.833	1.576	M A A	Weight 83 pounds (37.6 Kg.), sputum negative, Was- sermann negative
	11/23/26		40.8	4.7	8.1	0.283	2.806	8.120	1.892	M A A	Chemical improvement
	12/14/26		38.7	5.53	11.8	0.301	2.635	7.727	1.932	M A A	Weight 98.5 pounds (44.7 Kg.), discharged 12/24/26

TABLE 4—Observations on Blood in Men with Pulmonary Tuberculosis

Case	Date	Age	Cor- puscle Volume, Erythro- cytes Per- centage	Leuko- cytes 10 ³	Hemo- globin, Tail- qvist Test	Per- cent- age of Fibrin- ogen	Per- cent- age of Albu- min	Per- cent- age of Glob- ulin	Total Percent- age of Serum Albumin and Globulin	Ratio of Albumin to Globulin	Choles- terol Mg per 100 Cc	National Tuberculosis Asso- ciation Classifi- cation	Comment
35	7/ 8/26	17	40.6	8.95	70	0.452	4.365	4.090	8.455	1.067	141.7	F A C	Sputum positive, Wassermann negative, died 9/16/26
36	7/ 20/26	17	34.7	12.75	70	0.490	4.846	4.725	9.571	1.026		F A C	Sputum positive, Wassermann negative, discharged 9/1/26, bilateral cavities
37	2/ 4/26	28	34.0	15.85	65	0.609	2.997	5.244	8.241	0.572		F A C	Sputum positive, Wassermann negative, discharged 5/1/26, unimproved
38	6/22/26	28	31.4	16.65	65	0.604	4.074	4.665	8.739	0.873	106.1	F A C	Sputum positive, Wassermann negative
39	8/31/26	23	33.6	18.55	75	0.508	5.414	2.768	8.212	1.937	191.0	F A C	Sputum positive, Wassermann negative, acute exudative
40	10/ 4/26	26	36.2	16.4		0.686	4.489	3.157	7.616	1.12	163.0	F A C	Sputum positive, Wassermann negative
41	12/ 3/26	20	44.5	16.55	75	0.580	4.783	3.029	7.812	1.579	172.5	F A C	Sputum positive, Wassermann negative
42	3/18/27	40	42.7	15.75	75	0.493	4.30	3.679	7.979	1.087	159.0	F A C	Sputum positive, Wassermann negative
Average						0.560	4.374	3.920	8.294	1.199	155.5		
43	8/20/26	21	38.0	11.4	85	0.537	4.602	3.267	7.839	1.442	187.6	F A B	Sputum positive, Wassermann A C, died 11/22/26
44	8/ 6/26	27	53.3	17.1	65	0.482	4.660	3.141	7.801	1.483		F A B	Sputum positive, Wassermann negative, tuberculous enteritis, died 3/25/27
45	4/ 1/27	25	45.2	11.1	75	0.452	3.985	2.828	6.813	1.409	162.2	F A B	Sputum positive, Wassermann negative
46	6/21/26	28	39.9	6.2	75	0.547	4.313	4.930	9.243	0.875	162.8	F A B	Sputum negative, Wassermann 4 plus, pleuritic effusion
47	6/22/26	21	29.5	7.15	70	0.657	3.957	4.870	8.227	0.813	121.7	F A B	Sputum positive, Wassermann negative, epididymitis, died 9/20/26
48	12/16/26	17	36.4	17.55	65	0.607	4.231	2.607	6.840	1.623	153.9	F A B	Sputum positive, Wassermann 2 plus
49	5/17/26	22	31.2	17.85	60	0.490	3.395	5.051	8.446	0.672		F A B	Sputum positive, Wassermann 2 plus, discharged 10/6/26, quiescent
50	12/ 3/26	27	46.7	6.8	80	0.288	4.472	3.422	7.891	1.886	214.3	F A B	Sputum positive, Wassermann negative
51	3/18/27	33	25.6	11.8	60	0.810	3.550	5.147	8.697	0.689	152.3	F A B	Sputum positive, blood in urine
52	6/11/26	31	36.5			0.613	3.850	3.735	7.591	1.033	176.9	F A B	Sputum positive, milary tubercles on tongue, died 8/12/26
53	2/ 4/26	17	45.4	13.8	70	0.619	3.108	4.235	7.343	0.734		F A B	Sputum positive, Wassermann negative
Average						0.558	4.012	3.930	7.942	1.105	165.2		
54	8/17/26	23	40.6	13.8	80	0.401	5.500	2.193	7.693	1.888	150.2	F A A	Sputum positive, Wassermann negative
55	10/28/26	36	43.8	16.9		0.482	5.670	2.679	8.349	2.117	176.5	F A A	Fibroid, sputum positive, Wassermann 4 plus
56	12/ 8/26	35	44.5	7.75	70	0.535	5.190	2.180	7.370	2.380	171.4	F A A	Sputum positive, Wassermann negative
Average						0.472	5.453	2.851	7.804	2.128	160.1		
57	8/17/26	42	40.5	13.1	70	0.581	5.610	3.213	8.823	1.747	174.0	M A B	Sputum positive, Wassermann negative
58	11/ 4/26	20	35.9	15.1	75	0.410	5.212	2.704	7.916	1.909	180.7	M A B	Sputum positive, Wassermann negative, discharged 3/26/27, improved
59	12/20/26	19	41.5	18.6	75	0.508	4.490	2.547	7.037	1.763	183.0	M A B	Sputum positive, Wassermann negative
60	2/10/27	26	43.8	16.3	75	0.390	5.365	2.283	7.618	2.350	181.4	M A B	Sputum positive, Wassermann negative
61	12/ 6/26	22	42.4	13.95	70	0.505	4.564	2.980	7.544	1.532	166.7	M A B	Sputum positive, Wassermann negative, 4/1/26, M A A
62	12/ 6/26	24	48.4	14.05	65	0.429	4.661	3.031	7.692	1.538	156.3	M A B	Sputum positive, Wassermann negative, discharged 4/8/27, improved
63	7/ 6/26	23	41.3	5.3	85	0.458	4.955	4.254	9.209	1.165	165.5	M A B	Sputum negative
64	3/18/27	18	37.5	12.95	65	0.566	3.831	3.553	7.384	1.078	115.2	M A B	Sputum positive, Wassermann negative
65	3/18/27	33	44.2	10.15	75	0.521	4.910	2.873	7.783	1.719	158.0	M A B	Sputum positive, Wassermann negative
Average						0.484	4.844	3.048	7.893	1.644	164.5		
66	12/ 3/26	31	44.4	15.85	70	0.407	5.445	3.553	8.998	1.532	192.7	M A A	Sputum positive, Wassermann negative
67	2/20/26	33	35.4	19.52	65	0.613	3.350	4.095	7.440	0.819		M A A	Sputum positive, Wassermann negative, developed diarrhea, died 7/25/26
68	7/19/26	22	40.2	9.7	85	0.513	5.069	4.249	9.318	1.193		M A A	Sputum positive, Wassermann 4 plus
69	3/14/26	30	47.8	9.85	75	0.309	4.890	2.331	7.221	2.698	206.5	M A A	Sputum positive, Wassermann negative
Average						0.470	4.688	3.556	8.244	1.410	199.6		
70	1/25/27	30	44.8	7.0	70	0.462	4.510	3.020	7.530	1.502	190.6	M A A	Sputum positive, Wassermann negative
71	7/20/26	34	47.9	8.7	85	0.269	5.820	2.422	8.242	2.403	192.3	M A A	Sputum negative, Wassermann negative, discharged 12/5/26, improved
Average						0.365	5.165	2.721	7.886	1.952	191.4		

TABLE 5—Observations on Blood in Men with Pulmonary Tuberculosis

Case	Date	Age	Cor- puscle Volume, Erythro- Per- centage	Leuko- cytes 10 ³	Hemo- globin, Tall- qvist Test	Per- cent age of Fibrin ogen	Per- cent age of Albu- min	Per- cent age of Glob- ulin	Total Percent age of Serum Pro- teins	Ratio of Albumin to Globulin	National Tuberculosis Asso- ciation Classification	Comment	
82	2/ 1/23	27	41.7	5.62	16.7	70	0.551	2.989	4.604	7.593	0.649	F A C	Sputum positive, Wassermann negative
	8/26/26		36.1	4.79	11.45	80	0.625	5.240	3.697	8.937	1.117	F A C	Sputum positive, improved
83	2/20/26	20	16.5	1.78	13.3	75	0.631	2.920	4.920	7.840	0.593	F A C	Sputum positive, Wassermann negative
	8/12/26		36.3	1.67	15.05	80	0.468	5.062	2.521	7.613	2.019	F A B	
84	1/26/26	32	42.0				0.613	3.169	6.831	10.300	0.508	F A C	Sputum positive, Wassermann negative
	8/26/26		36.7	4.71	17.85	80	0.521	4.508	3.825	8.333	1.179	F A A	
85	4/26/26	42	41.3	1.92	17.75	70	0.683	3.703	7.119	10.822	0.520	F A C	Sputum positive, Wassermann negative
	8/31/26		43.2	5.74	13.25	85	0.686	4.661	3.950	8.611	1.181	F A A	Discharged 12/2/26, improved
86	10/ 1/26	27	36.2	4.70	16.40		0.686	4.489	3.157	7.646	1.422	F A C	Sputum positive, Wassermann negative
	2/10/27		35.6	4.10	13.15	65	0.607	4.331	3.404	7.735	1.273	F A C	Some clinical improvement, laryngitis, sputum positive
87	6/10/26	44	45.4	4.87	16.25	75	0.461	3.928	3.886	7.814	1.011	F A B	Sputum positive, Wassermann negative
	10/15/23		42.3	6.22	13.2	85	0.462	4.720	3.390	8.110	1.361	F A B	Sputum positive, discharged 2/10/27, improved clinically
88	5/17/26	35	38.6	5.46	13.65	90	0.490	1.123	3.667	7.795	1.124	F A B	Sputum positive, Wassermann negative, weight 144 pounds (65.3 Kg)
	8/10/26		39.1	4.77	8.5	75	0.656	5.070	3.312	8.382	1.531	F A B	Weight 122.5 pounds (55.5 Kg), unimproved
	10/25/26		36.3	3.75	13.2		0.551	5.022	3.072	8.094	1.635	F A B	Sputum positive, weight 133.5 pounds (60.5 Kg), discharged 12/10/26, F A C
89	5/20/26	23	38.4	5.11	22.6	70	0.656	4.365	4.399	8.764	0.992	F A B	Sputum positive, Wassermann negative, weight 142 pounds (65.3 Kg)
	4/12/27		48.1	5.35	9.45	80	0.405	5.117	3.355	8.472	1.526	F A A	Sputum positive, discharged 9/23/26, quiescent
90	6/ 1/26	30	35.5	5.01	6.0	70	0.440	4.846	3.870	8.716	1.232	F A B	Sputum positive, Wassermann negative
	10/18/26		43.8	5.45	7.05	80	0.426	5.980	2.555	8.535	2.340	F A A	
91	7/ 6/26	18	39.5	4.65	13.4		0.446	5.445	3.228	8.673	1.687	F A B	Sputum positive, Wassermann negative, active
	1/ 4/27		41.1				0.331	4.890	2.182	7.072	2.240	F A C	Pneumothorax case, sputum positive
92	7/ 6/26	25	36.6	4.4	8.0	80	0.394	5.119	3.435	8.554	1.578	F A B	Sputum negative, Wassermann negative, pleural effusion
	1/ 4/27		46.6				0.369	5.117	2.578	7.695	1.985	F A A	Sputum negative
93	7/ 8/26	21	38.1	4.74	14.0	70	0.537	4.280	3.750	8.030	1.141	F A B	Sputum positive, Wassermann negative
	12/20/26		42.8	5.28	13.1	75	0.497	4.762	2.415	7.177	1.972	F A A	Sputum positive, discharged 12/22/26, improved

94	12/ 8/26	20	10.0	4.46	13.0	70	0.559	4.826	2.780	7.606	1.736	155.4	F A B	Sputum positive, Wassermann negative, laryngitis
	2/10/27		32.4	3.92	12.95	60	0.389	3.227	2.778	6.005	0.860	130.8	F A C	Died 2/18/27
95	6/ 4/26	27	43.4	4.21	13.0		0.455	4.331	3.987	8.318	1.086	244.5	F A A	Sputum positive, Wassermann negative, gonorrhea
	10/26/26		40.7				0.350	5.789	2.867	8.656	2.018	236.8	F A A	Sputum positive
96	7/16/26	25	38.3	5.19	9.35	80	0.375	4.527	4.346	8.873	1.042	171.8	F A A	Sputum positive, Wassermann negative
	10/21/26		33.9	4.96	10.25	75	0.370	4.680	2.710	7.390	1.727	155.2	F A A	Sputum positive
97	7/16/26	40	38.5	4.82	11.45	80	0.509	4.365	3.305	8.670	1.014	175.8	F A A	Sputum positive, Wassermann negative
	10/21/26		37.9	4.1	16.4		0.465	4.450	3.085	7.535	1.443	182.9	F A B	Sputum positive
98	7/16/26	45	37.3	4.94	10.35	85	0.525	4.264	2.873	7.133	1.485	267.9	F A A	Sputum positive, Wassermann negative
	11/ 4/26		44.8	5.11	9.2	80	0.410	5.274	2.402	7.676	2.197	202.8	F A A	Sputum positive, improvement
99	7/14/26	23	13.2	5.32	8.15	80	0.547	4.215	3.041	7.266	1.387	190.6	M A B	Sputum positive, Wassermann negative
	11/23/26		43.3	4.82	13.6	80	0.542	5.023	2.394	7.417	2.098	173.1	M A B	Sputum positive, discharged 11/26/26
100	7/16/26	30	34.8	4.46	12.6	80	0.452	4.400	4.861	9.231	0.905	222.8	M A B	Sputum positive, Wassermann negative
	3/14/27		45.5	4.6	8.75	70	0.326	4.681	2.742	7.423	1.707	208.0	M A A	Sputum positive, marked improvement
101	9/27/26	23	46.4	4.81	13.25	75	0.542	4.805	3.160	7.965	1.520	176.5	M A B	Sputum positive, Wassermann negative
	4/ 4/27		50.0	5.80	12.55	75	0.465	4.533	2.401	6.984	1.910	159.5	M A B	Sputum positive, Wassermann negative
102	10/ 4/26	29	37.3	4.40	9.8	80	0.458	5.167	2.216	7.333	2.279	236.9	M A B	Sputum positive, Wassermann negative
	4/ 6/27		43.1	5.07	13.8	80	0.455	4.838	2.606	7.471	1.868	192.3	M A B	Sputum positive, Wassermann negative
103	8/12/26	27	30.5	3.86	7.05	80	0.547	4.846	2.895	7.741	1.674	261.7	M A C	Sputum positive, Wassermann negative, adenitis
	12/13/26		40.2	5.17	6.5	80	0.493	5.070	2.807	7.877	1.806	187.5	M A A	Discharged 9/10/26, quiescent
104	12/ 8/26	30	51.3	5.32	17.35	80	0.537	4.826	3.060	7.886	1.577	172.4	M A B	Sputum positive, Wassermann negative
	4/ 6/27		51.0	6.53	12.2	90	0.375	4.933	2.417	7.350	2.042	192.0	M A A	Discharged 4/9/27, improved
105	10/28/26	40	35.8	5.33	11.1	80	0.575	4.365	3.304	7.069	1.321	176.5	M A A	Sputum positive, Wassermann negative
	4/ 4/27		42.2	5.8	16.02	70	0.656	3.956	3.183	7.142	1.242		Mn B	Sputum positive
106	11/ 4/26	23	43.5	4.85	14.1	70	0.497	4.680	3.196	7.876	1.464	174.4	M A A	Sputum positive, Wassermann negative
	4/ 4/27		36.2	5.37	15.62	75	0.432	4.680	2.401	7.081	1.950	158.0	M A A	Sputum negative, discharged 2/26/27, arrested
107	6/ 4/26	23	41.5	5.08	11.3	70	0.410	4.847	3.960	8.807	1.259	161.5	M A A	Sputum positive, Wassermann negative, weight 115 pounds (65.8 Kg)
	10/21/26		39.6	4.51	10.7	70	0.362	4.720	2.805	7.525	1.677	193.9	M A A	Sputum negative, discharged 12/11/26, quiescent
108	9/27/26	20	41.9	5.3	9.2		0.402	5.100	1.975	7.165	2.628	172.4	Mn B	Sputum positive, Wassermann negative
	2/17/27		46.1	5.33	8.7	78	0.298	4.846	2.495	7.841	1.942	193.9	Mn A	Sputum negative, discharged 2/26/27, arrested
109	8/24/26	21	14.2	5.23	9.7	80	0.443	5.500	2.333	7.833	2.357	300.0	Mn B	Sputum positive, Wassermann negative
	4/ 6/27		48.1	5.55	11.7	77	0.469	5.365	2.283	7.648	2.350	263.1	Mn B	Sputum negative, quiescent

butter, since the level of cholesterol in the blood and likewise in the tissues can be raised through the feeding of cholesterol or foods rich in cholesterol

CONCLUSIONS

The data given in the tables justify the following conclusions. First, with a subnormal cholesterol content, clinical improvement is accompanied by an increase in blood cholesterol (table 5, patients 84, 85, 88, 89, 93 and 104), while the reverse can be observed in patients 94 and 96 (table 5). Second, a stationary or increasing hypercholesterolemia in tuberculosis indicates immunity and resistance, and a falling hypercholesterolemia indicates the opposite.

Fibrin, a plasma globulin, is a labile substance compared with the other blood proteins. Since it reacts to a multitude of stimuli within the body, an individual fluctuation of from 20 to 25 per cent is considered within normal limits. The only factors that have been proved to influence fibrin content are food, hemorrhage, inflammation, injury to tissue and certain general intoxications which do not cause any obvious injury to cells. The increase in fibrin found in tuberculosis may be due to injured tissue, to the familiar inflammation which usually accompanies extensive tissue injury and to the presence of pathogenic organisms, although Foster and Whipple⁷ conclude that bacteria are not directly concerned in this reaction, since fibrin values are identical in blood whether a sterile or a septic inflammation is present. This conclusion seems to account for the results obtained from a comparison of the fibrin values and the leukocyte count, namely, all patients with a high leukocyte count have a high fibrin value (table 2, patients 16, 3, 10, 27, 14), but the high leukocyte count does not in all instances accompany a high fibrin (table 2, patients 24, 25, 33, table 4, patients 46, 47, 56). Since injury to tissue is the most powerful single stimulus to the overproduction of fibrinogen in the blood, it follows that the quantity of fibrinogen is a direct measure of the amount of tissue undergoing active destruction. This accounts for the fact that often fibrinogen is as high in the moderately advanced or incipient type of tuberculosis as in the far advanced cases.

Serum proteins under ordinary conditions in the individual case are relatively constant, but may vary, particularly in disease. A disturbance in the concentration of the albumin and the globulin occurs in tuberculosis—a condition which is difficult to explain, since little is known of the exact function of the proteins in the blood.

The fluctuations of serum proteins in tuberculosis were found to be an increase in the globulin fraction with a decrease in the albumin

⁷ Foster and Whipple. Blood Fibrin Studies, *Am J Physiol* **58** 408 (Jan) 1922

in the majority of cases, and a normal or slightly increased total protein, especially in the far advanced type. The increase in globulin may be due to the body's resistance to infection, to formation of toxins, or to a development of immune bodies. Moll⁸ found a similar increase in globulin in animals injected with various proteins, gelatin and killed bacteria. The usual decrease in the albumin may be partially the result of the body's attempt to reduce the osmotic pressure of the blood. Additional factors evidently are involved, otherwise the albumin would decrease more than has been observed in order to equalize the increase in the osmotic pressure caused by the increase in globulin. The percentage increase in globulin is about six times the percentage decrease in albumin, although the globulin molecule is approximately only twice the molecular weight of the albumin molecule.

The fluctuation in the total protein content cannot be ascribed alone to changes in the water content of the blood and tissues, since the changes in the individual fractions are not simultaneous. The usual sequence is an increase in fibrinogen, later an increase in globulin, followed by a decrease in albumin. These changes represent true alterations in the protein content and are not the result of simple fluctuations in the water content, although any disturbance in the water balance must have its effect on the concentration of the constituents of the blood.

SUMMARY

Chemical studies in tuberculosis demonstrated the following facts

- 1 The cell volume is usually below normal, especially in active cases with much emaciation
- 2 The size of the erythrocyte is decreased
- 3 The cholesterol content of the blood may be increased or decreased
- 4 A rising or stationary hypercholesterolemia indicates resistance and immunity, while a falling hypercholesterolemia or a hypocholesterolemia represents a lowering in resistance and immunity
- ✓ 5 ~~Fibrinogen is increased in proportion to the amount of tissue undergoing destruction~~
- 6 The globulin values are definitely increased, associated with a smaller percentage decrease in the albumin
- 7 The total serum proteins are normal or hypernormal, the increase being due to the high fraction of globulin

⁸ Moll Beitr z Chem Phys u Path 4 563, 1903

POSTURAL TREATMENT OF LUNG SUPPURATION

A NEW POSTURAL FRAME, THE JACK-KNIFE POSITION AND
ABDOMINO-DIAPHRAGMATIC PULMONARY COMPRESSION,
WITH A REVIEW OF THE LITERATURE¹

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Postural treatment, though recognized as decidedly valuable in pulmonary suppurative conditions, has not received the attention it deserves. Considering its importance, it is surprising that not only clinicians, but also bronchoscopists and thoracic surgeons have not taken advantage of and put into more general use a procedure having merited value.

Considering the possession of the knowledge by primitive peoples of the value of the use of the upside-down position for emptying the lungs of inspired water in cases of drowning, as well as the more modern methods of Marshall Hall, Sylvester, Howard and Schaefer, it is surprising that the scientific and practical value of posture for evacuating purulent accumulations in the lungs was not commonly recognized until about twenty-five years ago. It is difficult to understand that it was not until the decade just passed that the principle of postural drainage for lung suppuration began to find advocates and the knowledge of its value became popularized.

REVIEW OF LITERATURE

A search of the literature reveals a strikingly small number of articles on this subject. Only a few of these are devoted exclusively to the description, consideration and advocacy of postural methods, several authors cite cases in which patients were cured by this means, while others simply quote case reports with results obtained, or casually mention the value of posture as an additional aid in the treatment of patients with suppurative conditions of the lungs. With few exceptions, textbooks are silent on this mode of treatment, some merely mention it in passing and do not give a description of the method or the manner of application.

That pulmonary suppuration was not unknown in antiquity is evidenced by mention by Hedblom¹ of the teaching of that wise old master-physician, Hippocrates (quoted by Koch), who demonstrated that a pulmonary abscess that had burst into the pleural cavity could be healed

¹ From the Bronchoscopic Division, Hospital for Joint Diseases

1 Hedblom, C. A. Pulmonary Suppuration, M. Rec. 96 442 (Sept. 13) 1919

by draining the latter. It was Laennec,² however, who first placed pulmonary disease on a reliable basis, and who differentiated bronchiectasis (first noted by his assistant Cayol in 1808), pneumothorax, hemorrhagic pleurisy, gangrene and emphysema of the lungs, esophagitis and chronic diffuse interstitial hepatitis.

In 1898, von Quincke (according to Schaefer³) was the first to treat patients who had bronchiectasis by using the oblique position, and to him, apparently, belongs the credit of first placing the treatment for pulmonary suppurative conditions by postural methods on a scientific basis.

A cure of abscess of the lung by postural treatment was reported in 1912 by McKechnie.⁴ He reported the case of a boy, aged 14. The diagnosis was abscess of the liver, with perforation of the diaphragm and pleura and secondary abscess at the base of the lung. If this condition were present, there was little hope that the cavities could be healed under ordinary circumstances. The boy was suspended over the edge of a table, head downward, the whole body hanging vertically upside down, the legs and thighs lying on the table at right angles to the body and thus supporting him. In this position he was made to cough and to squeeze the chest until no more pus came out. The process was repeated five or six times daily, and by this means the abscess cavity was completely emptied. Progress was remarkable, in six weeks the boy was cured without operation of a condition which had lasted five years, and which had baffled other modes of treatment. McKechnie advocated the use of this method before recourse is made to surgery.

In 1913, Garre and von Quincke⁵ stated that in the case of cavities in the lower lobe, expectoration is furthered most effectually by the patient's lying flat or with the shoulders at a lower level (several times a day from one to three hours, the morning hours are the best—from 5 to 9 or from 6 to 9—and in the evening from 5 to 7), in other cases tests must be made to find the most suitable position.

In 1915, Lord⁶ stated that the effect of posture should invariably be given a thorough trial. Evacuation may be favored if the patient lowers his head over the edge of the bed during a paroxysm of coughing. At stated intervals for a certain period the patient should lie with the affected side uppermost for the purpose of draining the pus into the

2 Laennec. Garrison's History of Medicine, 1921.

3 Schaefer, H. Postural Treatment of Bronchial Disease, *Klin. Wchnschr.* 2: 252 (Feb. 5) 1923, *J. A. M. A.* 80: 1493 (May 19) 1923.

4 McKechnie, W. E. Abscess of the Lung and Liver. Simple Cure of a Chronic Case by the Upside-Down Position, *Lancet* 1: 865 (March 30) 1912.

5 Garre and von Quincke. Treatment of Pulmonary Suppurations. Translated by D. M. Barcroft, Ed. 2, New York, William Wood & Company, 1913.

6 Lord, Frederick Taylor. Empyema and Pulmonary Abscess, *Boston M. & S. J.* 173: 798, 1915.

trachea Elevation of the foot of the bed for a time night and morning, with the patient lying at full length on the back or abdomen, and without a pillow, should be tried

DeJong,⁷ in 1918, reported a case of bronchiectasis of several months' standing The cough was distressing and the sputum was extremely malodorous, but no tubercle bacilli were found One lung seemed normal, but the temperature remained subfebrile The man was in the hospital for nearly four months, he steadily grew weaker, and there seemed to be no hope that an operation could be performed Then deJong raised the foot of the bed 40 cm, and administered potassium iodide freely At first this slanting position was maintained only one hour in each four, but the benefit was so prompt and so marked that the man begged to have the bed kept slanting all the time The expectoration diminished, the cough subsided and in seven weeks the man left for his farm, his health completely restored One young girl given similar treatment was in robust health several years later The iodide and copious drinking diluted the sputum, and the sloping position ensured its expulsion The position treatment should be given a trial first Zaaijer (quoted by deJong) has reported a case in which a young woman with bronchiectasis happened incidentally to discover the relief from lying with the shoulders low, and she spontaneously assumed this position every morning

In 1919, Hedblom,¹ in an article to which is appended a complete bibliography on lung suppuration, mentioned that patients often discover that certain positions favor expectoration and unconsciously make use of gravity to help empty the cavity That spontaneous cures occur in this manner is to be expected He also stated that patients have been cured even of abscesses perforating from the liver by promoting gravity drainage (quoting McKechnie's⁴ case) Recently, von Deeston⁸ reported a similar case in which a perinephritic abscess ruptured into a bronchus Patients with acute cases of a mild type may be treated expectantly for a few weeks in the hope that drainage through a bronchus may effect a cure The mortality following expectant treatment at first was high

Wessler⁹ also, in 1919, while recognizing the value of postural drainage, did not believe it exerted a curative effect At that time, he wrote that "the *medical* treatment for suppurative disease of the lung offers little that is encouraging" He believed that constant violent coughing,

7 DeJong, H Treatment of Bronchiectasia, *Nederl Tijdschr v Geneesk* **1** 495 (Feb 16) 1918, abstr, *J A M A* **70** 1343 (May 4) 1918

8 Von Deeston, H T Recumbent Posture Cough with Purulent Expectoration, *J A M A* **88** 98 (Jan 8) 1927

9 Wessler, Harry Suppuration of the Lung A Study of 100 Cases, *J A M A* **73** 1818 (Dec 27) 1919

by projecting the infectious material farther down into the smaller bronchi, undoubtedly disseminated the disease, and promoted the formation of bronchiectasis. He also said, however, that periodic upsetting of the patients will facilitate drainage, and irrigation of the bronchi through the bronchoscope accomplishes the same purpose. He thought, however, that this procedure cannot cure these patients, as it does not have any effect on the pulmonary infiltration. (This contention, however, has recently been disproved by repeated physical examinations and roentgenograms of many patients treated by postural means over a long period.)

Of course, there are many chronic cases of long duration in which extensive fibrosis and other infiltrative changes have taken place that neither postural nor any other form of treatment will influence. The early institution of postural treatment plus all other properly selected and applied means will prevent the formation and aid resolution of considerable peribronchial infiltration and early fibrosis.

In 1920, Lehmann¹⁰ advocated the use of the postural method, stating that the suspension method aided by procuring better drainage. In 1922, Carmody¹¹ advocated rest in bed for patients suffering from pulmonary suppuration with the foot of the bed elevated for postural treatment.

In 1922, Graham and Singer¹² advocated postural drainage as a method that often relieves a great many of the distressing symptoms by allowing large quantities of discharge at one time. This, of course, leaves the patient free from symptoms for hours at a time, and occasionally is sufficient to cause symptomatic cure. It was their impression that at best it is only a palliative method.

In 1923, Lukens, Moore and Funk¹³ in an article on bronchoscopic treatment of lung suppuration, stated that in addition to bronchoscopic drainage, the best possible natural drainage can be secured by having the patient sleep on the "well" side and assume this position as much as possible during the day.

Schaefer¹⁴ again reported the use of postural treatment in bronchial disease during the previous year. He used von Quincke's method in eleven cases, those of seven men and four women, with the most satisfactory results.

10 Lehmann, J. E. Lung Abscess, *Canad. M. A. J.* **10** 1090 (Dec.) 1920.

11 Carmody. Suppurative Conditions of Lung, *New York M. J.* **15** 742 (June 21) 1922.

12 Graham, E. A., and Singer, J. J. New Treatments of Bronchiectasis, *J. Missouri M. A.* **19** 390 (Sept.) 1922.

13 Lukens, R. M., Moore, W. F., and Funk, E. H. Bronchoscopic Drainage of Pulmonary Abscesses and Bronchiectasis, *M. Clin. N. Amer.* **6** 1015 (Jan.) 1923.

14 Schaefer, H. *Presse med.* **3** 109 (Feb. 3) 1923.

Whittemore¹⁵ also prefers to give each patient a chance to cure himself by postural drainage and by building up his general condition before operation is advised

In 1924, Lambert and Miller¹⁶ advocated postural treatment for abscess of the lung. Their method consists of rest and postural drainage, the latter carried out four or five times daily for periods varying from five to twenty minutes each. Postural drainage is carried out by the patient hanging over the side of the bed with the head to the floor. This position is maintained from three to five minutes at first, as the patient becomes accustomed to it, the time is increased to as long as may be necessary to empty the abscess cavity thoroughly, usually from ten to fifteen minutes for each drainage. By this method it is possible to increase materially the number of cures by spontaneous drainage through a bronchus. Medical treatment for from three to four weeks can usually be safely employed to determine the necessity for operation.

In 1924, Moore,¹⁷ after outlining the technic of bronchoscopic treatment for suppurative disease of the lungs said: "These patients are carefully instructed to aid, by posture, the drainage of the affected area."

In 1924, Weinberger¹⁸ reported a remarkable improvement in the condition of a girl with bronchiectasis. An artificial pneumothorax made the situation worse. The successful outcome is attributed to von Quincke's slanting position used gradually for several hours daily.

In the same year, Mackey¹⁹ reported complete recovery by postural drainage of a large abscess of the lung without surgical intervention.

In 1924, Dorendorf²⁰ observed spontaneous recovery in nineteen of his thirty-one cases of abscess of the lungs after influenza, nine patients, four of whom died, required an operation. Three of the other cases ended fatally. He attributes his nineteen cures to simple treatment—von Quincke's advice of a posture which facilitates evacuation of the pus, and restriction of fluid intake.

In 1926, Castlen²¹ advocated the early institution of postural drainage for abscess of the lung by elevation of the foot of the bed or hips, or by the use of a special table, before resorting to more radical measures.

15 Whittemore. Treatment of Non-tuberculous Pulmonary Abscess, Boston M & S J **188** 477 (April 5) 1923

16 Lambert, Adrian, V. S., and Miller, James Alexander. Abscess of Lung, Arch Surg **8** 446 (Jan.) 1924

17 Moore, W. Frederick. The Bronchoscopic Treatment of Suppurative Disease of the Lungs, J A M A **82** 1036 (March 29) 1924

18 Weinberger, R. Bronchiectasis, Wien klin Wchnschr **37** 1067 (Oct. 9) 1924

19 Mackey. International Medical & Surgical Survey (Med. 1066, Nov.) 1924

20 Dorendorf, H. Influenza and Lung Abscess, Med Klin **20** 1233 (Sept. 7) 1924

21 Castlen, C. R. Pulmonary Abscess, Northwest Med **25** 294 (June) 1926

In a recent article, Lambert²² stated that "the crux of the successful treatment of lung abscess may be summed up by the one word 'drainage,' and in the management of any given case the problem is to effect adequate drainage." He also emphasized that 50 per cent of all patients recovered completely under the more conservative forms of treatment without operation.

Miller,²³ while speaking of abscess of the lung said

The primary and basic treatment is absolute bed rest combined with postural drainage. This combination of rest and postural drainage constitutes, therefore, our basic method of treatment, to be first used in practically all cases, and the result obtained affords a point of approach to the consideration of additional methods which may be necessary. In our experience about twenty per cent of all cases are cured by these methods alone.

His description of the use of postural drainage is one of the best written thus far and should be read in the entirety by those interested in this method of treatment.

Since 1924, however, most of the writers previously quoted in subsequent articles and many surgeons who specialize in operations on the lungs mention the efficacy of postural treatment in pulmonary suppurative conditions, and advocate its trial preliminary to operative intervention.

This completes a rather careful survey of the literature. No doubt many cases in which the patients were cured by postural drainage have not been reported, and many more patients whose cases were unrecognized have been cured by spontaneous evacuation, postural or otherwise. Thus I believe sufficient evidence of the value of postural drainage in pulmonary suppuration has been adduced by reliable workers in this field.

METHODS AND APPARATUS USED IN TREATMENT

It has frequently been noted that patients suffering from conditions of this kind accidentally discover that certain positions materially aid in ridding them of excessive accumulations of bronchial pus.

A prime requisite for gravitational relief is a nonobstructed outlet from the region of the abscess, hence it is obvious that the theoretically ideal position for postural drainage would be a suspension of the patient by the heels with the head hanging down and with the body hanging in a straight line with the feet uppermost—standing on one's head, so to speak. The impracticability of such a posture precludes the use of this method.

Up to the present time, the von Quincke position has been considered the best possible means of postural drainage applicable to the average case.

²² Lambert, Adrian V. S. Pulmonary Abscess and the Treatment from the Surgical Standpoint, New York State J. Med. **27** 47 (Jan. 15) 1927.

²³ Miller, James Alexander. Medical Aspects of Abscess of the Lung, New York State J. Med. **27** 43 (Jan. 15) 1927.

The method of having the patient lie flat on the abdomen with his chest over the edge of the bed and his head hanging low, at best serves as a makeshift, the pressure of the body against the bed precluding free respiration by creating obstructive pressure against the sternum and ribs as well as preventing free play of the intercostal, diaphragmatic and abdominal muscles

The Jack-Knife Position—An intensive study of the inverted body position in order to determine what posture would allow a low hanging head and at the same time a free play of the respiratory muscles led to the adoption of what I have called the "jack-knife position," so-called because of its resemblance to a half-closed pocket knife. In order to permit an easy assumption of this posture and a prolonged period of suspension with the head low, it was found that having the patient hanging on a band across the groins, the body flexed forward on the thighs, and the head at the most dependent position, approached the ideal, as thus the chest and abdominal muscles are free from pressure and an "inverted bronchial tree" is created, the ideal position for drainage

Postural Frame for Body Suspension—To permit the patient to assume and maintain this position easily and safely, I had a body suspension frame constructed (fig 1). It consists of two U-shaped bent-pipe frames held together at their uppermost free ends by hinge-joints. Stretched horizontally between the upper joined ends of the frames is a stout chain covered with padded leather, across which one may hang at the groins with comfort. To prevent the side members from spreading from the weight of the body, a side bar is hooked from one side to the other.

Description of Use of Apparatus—On the floor directly under the patient's head a basin is placed to receive the expectorated secretions. The patient is instructed to assume the jack-knife position immediately on arising in the morning and before retiring at night. He remains in the suspended position for from fifteen to twenty minutes at each seance, hanging with head suspended for three minutes and standing upright for one minute, to relieve him from dizziness or other unpleasant sensations that might arise from the blood rushing to his head or from the unaccustomed position.

During the first few days it is best to have him remain suspended with the head low for one minute periods, with two minute intervals of the upright position. Patients quickly become used to the posture, and the relief afforded makes them cooperate readily.

If when the patient assumes this position the secretions are not readily coughed out, he is instructed to cough a few times. This usually suffices to stimulate the cough reflex, and the retained secretions are ejected.

Abdominodiaphragmatic Pulmonary Compression—Of additional value in aiding the patient to empty the purulent secretions, and possible only in the jack-knife position, is "abdominodiaphragmatic pulmonary compression." This is accomplished as follows. After the patient has evacuated as much secretion as possible by coughing, and while he is still in the suspended position (fig 4), the physician stands behind the patient and (fig 2) places his hands on the back of the patient's thighs near the popliteal regions, and a nurse, who stands in front of the patient, takes hold of his shoulders. The patient's body is then brought up into a nearly horizontal position (straightened out, fig 2). He is then told to take a slow deep inspiration and to hold his breath, then the physician and attendant simultaneously push toward each other, bringing the patient's knees toward his chin and flexing the body as one would close a pocket knife (fig 3), this is done in a firm quick manner. The muscles of the patient's abdomen become fixed, as does the diaphragm, and the forced flexion of the inflated chest on the thighs causes the diaphragm to press upward against the distended lungs, and whatever residual secretion remains in the lungs is readily expelled. This procedure is repeated once or twice during the first few treatments, and as the patient becomes accustomed to it, it may be repeated from six to eight times at each seance. In no other way can the lungs be so completely and efficiently emptied of retained purulent secretion.

CONCLUSION

As with abscesses in other regions the prognosis of abscess of lung depends mainly on the freedom with which the purulent accumulation can evacuate itself. The less often and the less complete the evacuation of pus, the longer the duration of the disease process and the less chance for a complete recovery either by natural (nonsurgical) means or by induced methods (surgical intervention).

The marvelous recuperative properties of the bronchopulmonary mucosa, as well as the healing powers of the pulmonary tissues themselves, are known to all. When the load is taken off the overwhelmed mucosal cilia, if they have not been completely destroyed, and when mechanical obstructions such as granulations and cicatrices, do not mechanically constrict the bronchial canals, resolution takes place with astonishing rapidity. Should any of the latter complications be present, they should receive the proper bronchoscopic attention.

The frequent dramatic cures of abscess of the lung following spontaneous evacuation by way of the normal air passages are familiar to all clinicians. These desirable results are not limited to solitary abscess of the lung, but are obtained also in cases of multiple bronchiectatic abscesses. The percentage of spontaneous cures of solitary pulmonary accumulation of pus is considerably greater than the multiple or

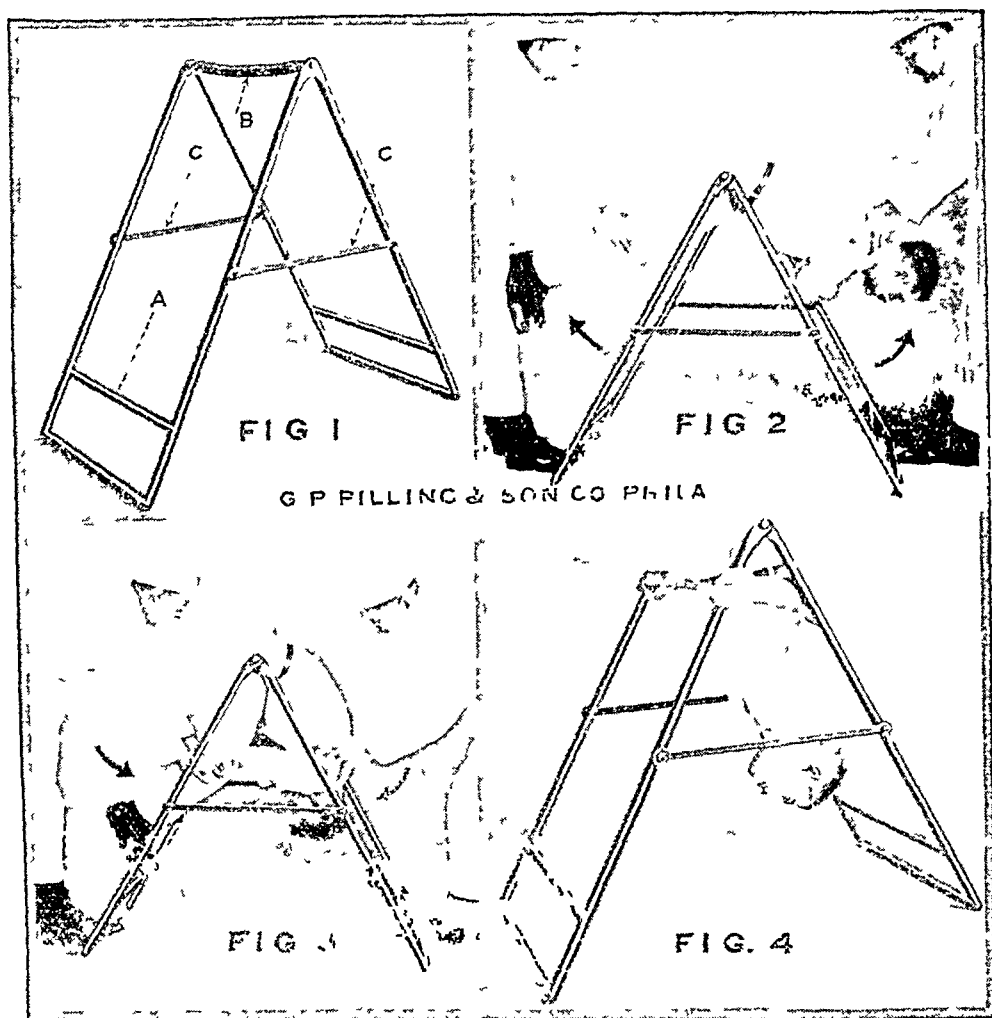


Fig 1—Postural body suspension frame for jack-knife position *A* indicates the metal step, *B*, the padded leather-covered chain and *C*, the metal side bars

Fig 2—The patient in extended position Note inflated chest and position of attendants' grasp The patient's body is carried upward in direction indicated by arrows

Fig 3—The patient in flexed (jack-knife) position After the body is brought into the position shown in figure 2, is told to take a deep breath and to hold it The body is then suddenly and somewhat forcibly flexed into the position indicated by the direction of arrows

Fig 4—The patient exercising without attendants Note the position of the limbs The patient brings thighs and legs downward flexing same on body With the chest inflated with air, the mouth open, and holding the breath, the jack-knife position is assumed in a rather forcible manner The sudden pressure of the diaphragm in the act of expiration forcibly exerts a sudden expulsive force by compressing the lungs and with the patient in the inverted posture, permits evacuation of a greater amount of bronchial secretion than any other postural means

bronchiectatic form. The earlier the diagnosis is made and the sooner proper therapeutic measures are undertaken, the greater the possibility of an earlier and nonsurgical cure. In a considerable proportion of cases the condition resists every form of nonsurgical treatment, and despite medicinal, dietetic (restriction of fluids), vaccinal, climatic, bronchoscopic (irrigation and suction) and endoscopic treatment (topical application or injection of the various medicaments used in these cases) and the early institution of postural treatment, the patients gradually become worse, and unless radical and at times even heroic measures are instituted, a fatal termination ensues. Patients with pulmonary suppurative conditions cannot be treated by "rule of thumb" methods. Each case must be individualized, and the patient treated according to its peculiar type.

I wish to emphasize the importance of the early recognition and correct diagnosis of pulmonary suppuration. It is astonishing how many cases are unrecognized even in well conducted clinics until the simpler methods of treatment are of no value.

The curative value of postural treatment for pulmonary suppurative conditions depends on its early institution. In general, it might be stated that the earlier postural treatment is instituted, the greater is the chance for nonsurgical cure, however, I do not wish to have it understood that I contend that postural treatment alone will accomplish a large percentage of cures. True, a small number of cures will occur by spontaneous evacuation through the normal air passages and a larger number by spontaneous evacuation plus postural treatment, just so, postural treatment plus all the other aids properly selected and properly applied at proper times will permit a still greater percentage of cures. The patient who does not obtain some relief by postural treatment is exceptional.

I believe that bronchoscopic study and the various bronchoscopic treatments take first rank among the nonsurgical means thus far devised for the expectant treatment of suppuration of the lung. Reference here is made, of course, to those cases in which the patient is not moribund, or which are not strictly surgical cases. There are, however, many so-called borderline cases which, though serious, occasionally escape the more radical thoracoplastic surgical procedures by postural and bronchoscopic treatment.

Postural Treatment and Bronchoscopic Irrigation—Postural treatment may be used without bronchoscopic irrigation, or if one favors the latter procedure for treatment in certain cases of pulmonary suppuration, it is of special value. If postural treatment is used before the bronchoscope is introduced, a considerable amount of the purulent material will be ejected, as a result, a smaller amount of irrigating fluid may be used, and it almost immediately comes in contact with the mucosa of the soiled but patent bronchi.

Again, postural treatment may be used to advantage after bronchoscopic irrigation. Following bronchoscopic irrigation and suction treatment for pulmonary suppuration, considerable free fluid remains in the bronchi, as is shown by the coughing and expectoration of varying amounts of an admixture of irrigating fluid, mucus, pus and often blood directly after such treatment. The utilization of the postural method immediately after the irrigation, and particularly the "jack-knife position," will enable the patient to free himself more easily and more completely from such residual fluids than would otherwise be possible.

Postural Drainage in Roentgen-Ray Study of Bronchiectasis—Recently Singer and Graham²⁴ advised that postural drainage be instituted in bronchiectatic cases after the first roentgenogram is taken. They stated that subsequent roentgenograms will give information concerning the relative size of the bronchiectatic area.

Postural treatment, like many other means advocated for the relief or cure of certain conditions, because of improper use or improper instruction in its use is condemned as of little or no value. For the best results, the postural treatment for drainage of pulmonary suppuration must be applied according to the special requirements of the case. The same manner of application, frequency and length of treatment will not do for every case.

Many patients discover certain positions, movements and exercises while in the jack-knife position that enable them to empty their bronchial tree more easily than by those described. They should be permitted to utilize these exercises when not too strenuous or injurious, in preference to the routine measures. If assistance is not available at home, the patient can be taught to practice the procedure alone. Daily exercises are a *sine qua non* for the best possible results from postural treatment, these should be taken morning and night when possible, if once a day only, experiment will teach the patient the best hour. My patients are encouraged to purchase the apparatus for home use when their means permit. Members of their families can easily be taught to apply the abdominodiaphragmatic pulmonary compression method.

Respiratory gymnastics in the treatment of pulmonary suppuration is gradually assuming the important position in our armamentaria that it deserves. Arguments against it because of danger of inducing extension of the disease by auto-infection by inspiration of infective material fails to hold ground in the light of recent investigations. The extension of "draining" or "drainable" abscess of the lung, simple or bronchiectatic, is limitable to the primarily affected areas, once drainage is established either by postural or by surgical means.

²⁴ Singer, J. J., and Graham, E. A. Roentgen-Ray Study of Bronchiectasis, *Am J Roentgenol* **15** 54 (Jan) 1926.

CLINICAL RESULTS WITH EPHEDRINE THERAPY

A REPORT OF SIXTY-TWO CASES

T L ALTHAUSEN, M D

AND

I C SCHUMACHER, M D

SAN FRANCISCO

Ephedrine is an alkaloid that was isolated from the plant *Ephedra vulgaris* by Nagai in 1887 and rediscovered by Chen in 1923. Decoctions of *Ephedra vulgaris* have been used in China for five thousand years for diaphoretic and antipyretic purposes and as a sedative in cough. At the time of the original discovery of the alkaloid, the attention of the investigators was focused mainly on its mydriatic properties. To Chen¹ belongs the honor of working out the complete pharmacology of ephedrine, which was found to be a sympathomimetic drug closely allied in its chemical constitution and physiologic action to epinephrine. Chemically, ephedrine differs from epinephrine in that it does not contain a phenolic hydroxyl group, but has an extra methyl radical which accounts for its more persistent effects and greater stability, permitting oral administration of the drug and sterilization of its solutions by boiling. The physiologic effects of ephedrine are similar to sympathetic stimulation and consist in a rise in blood pressure due to cardiac stimulation and vasoconstriction, inhibition of intestinal movement, relaxation of bronchial musculature and stimulation of the uterine musculature. When applied locally, ephedrine causes mydriasis without changes in accommodation, and rapid shrinkage of the nasal mucosa. Experiments on animals have proved it to be of low toxicity, and continued use has shown that injury to any organ or tolerance to the drug has not developed.

For details of the chemistry and pharmacology of ephedrine, the reader is referred to the original articles by Chen,¹ and by Chen and Schmidt²

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¹ Read before the Annual Meeting of the California State Medical Association in Los Angeles, April 25, 1927

1 Chen, K K. A Pharmacognostic and Chemical Study of Ma Huang, J Am Pharm A **14** 189, 1924, The Effect of Ephedrine on Experimental Shock and Hemorrhage, Proc Soc Exper Biol & Med **22** 203, 1924, The Effect of Repeated Administration of Ephedrine, *ibid* **22** 568, 1925, The Acute Toxicity of Ephedrine, *ibid* **22** 404, 1925, A Comparative Study of Ephedrine, Tyramine and Epinephrine, J Pharmacol & Exper Therap **28** 59, 1926

2 Chen, K K, and Schmidt, C F. The Action of Ephedrine. The Active Principle of the Chinese Drug Ma Huang, J Pharmacol & Exper Therap **24** 339, 1924, The Action and Clinical Use of Ephedrine, J A M A **87** 836 (Sept 11) 1926

The ephedrine, in the form of its crystalline hydrochloride, used in our study was obtained from Dr B E Read at the Peking Union Medical College by Dr W J Kerr, and at his instigation tried out at the University of California allergy clinic and in certain cases in the wards of the University Hospital. Its clinical effects were studied in the following conditions: chronic vascular hypotension, shock, bronchial asthma, hay-fever, toxic erythema, urticaria and angioneurotic edema.

HYPOTENSION

Chronic Vascular Hypotension—The use of ephedrine in hypotension naturally suggested itself as soon as it was learned from animal

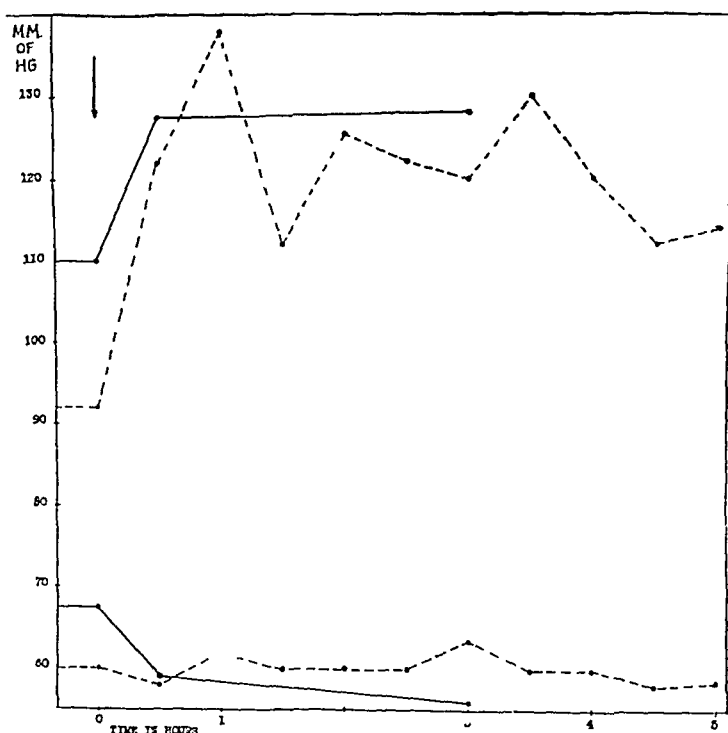


Chart 1—Curves showing blood pressure of patient number 39 (weight 147 pounds) after the administration of 25 and 50 mg of ephedrine by mouth. The solid line indicates the blood pressure after the administration of 25 mg of ephedrine, the broken line, after 50 mg. The arrow indicates when ephedrine was given.

experiments that this drug is capable of producing a sustained rise in blood pressure extending over a period of at least several hours.

Ephedrine was given to nine patients who had chronic vascular hypotension with a consistent systolic blood pressure of between 93 and 108. Eight of these patients were men, and one was a woman. All but three were hospital cases. In most cases the drug was given in doses of 50 mg, three times a day, by mouth. In all cases a rise in the systolic pressure amounting to between 9 and 46 mm was observed in from

five minutes to an hour, and the blood pressure remained above the initial level for four hours or more. The diastolic pressure was inconstant, but showed some rise in most cases. The variations of the diastolic pressure were between -10 mm and $+10$ mm. Charts 1 and 2 represent blood pressure curves in three patients with hypotension following the administration of ephedrine.

For comparison with the blood pressure curves of patients with vascular hypotension, the effects of ephedrine on normal blood pressures

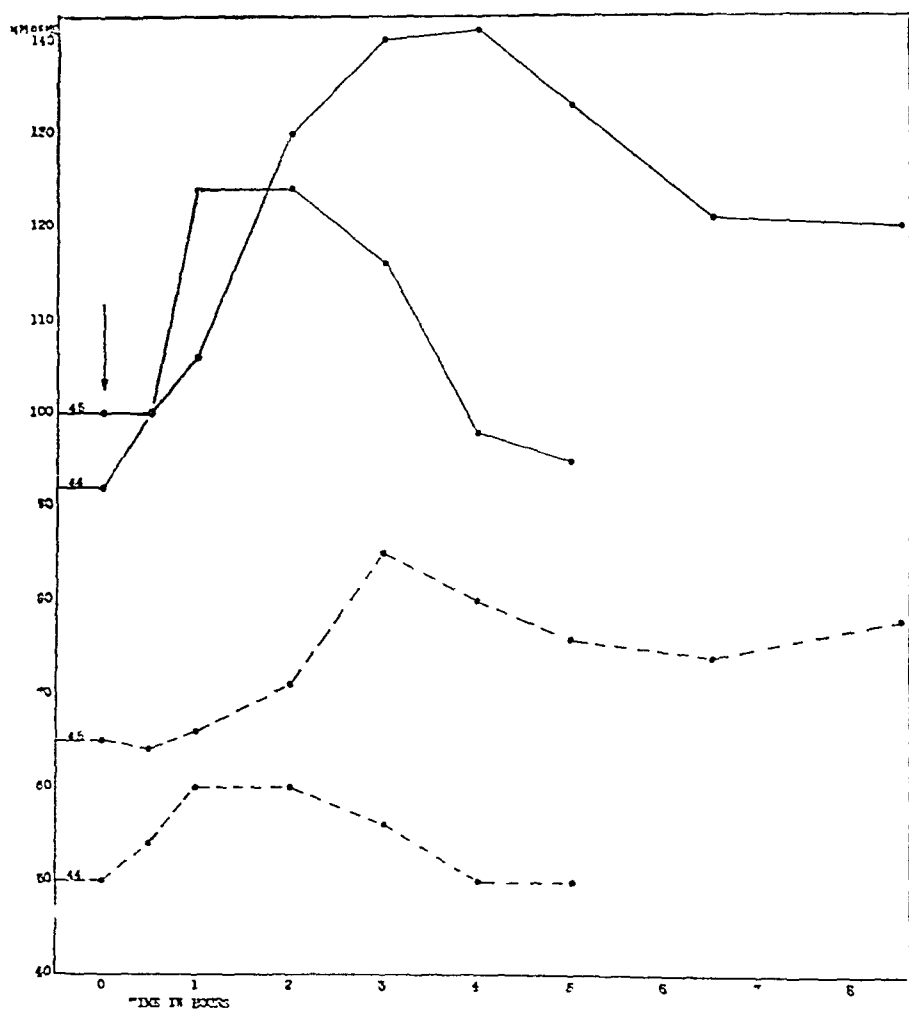


Chart 2—Curves showing blood pressure of patient number 44 (weight 124 pounds) and 45 (weight 143 pounds) after the administration of 100 mg of ephedrine by mouth. The solid line indicates the systolic blood pressure, the broken line, the diastolic. The arrow indicates when ephedrine was given.

were studied. The results as recorded in chart 3 show that these do not differ in any way from those in average cases of hypotension. It would appear that the amount of increase in the systolic blood pressure from ephedrine is independent of the weight of the patient, as suggested by the fact that a dose of 50 mg of ephedrine has increased the blood pressure by 9 and 44 mm in two patients weighing 95 pounds (43.1 Kg).

and 148 pounds (67.1 Kg), respectively, but that the same dose will produce the same increase in blood pressure on different days in the same person, and that the action of the drug is, within certain limits, roughly quantitative for the same patient. This can be seen from the fact that in case 39, the administration of 25 mg of ephedrine increased the systolic blood pressure by 18 mm, while 50 mg of ephedrine increased it by 46 mm, and in case 43 the increase after the administration of 50 mg was 10 mm, while after 75 mg it was 17 and 18 mm on two different days (charts 2 and 3). In cases 44 and 45, 50 mg of ephedrine raised the systolic blood pressure 14 and 15 mm, and 100 mg of the drug increased it 32 and 41 mm, respectively.

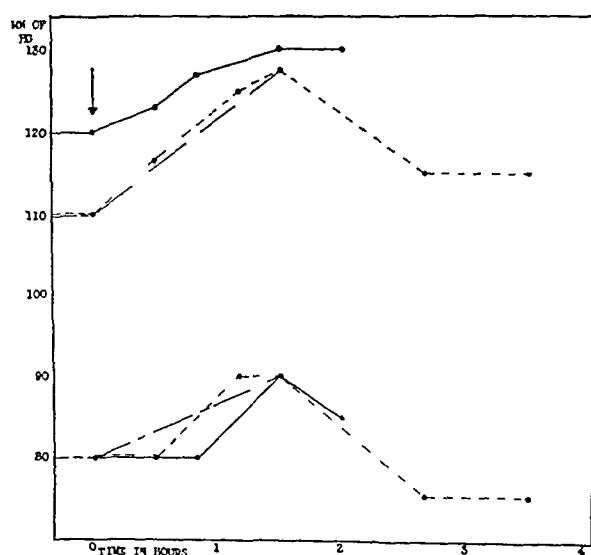


Chart 3—Curves showing blood pressure of patient number 43 (weight 179 pounds) on successive days after the administration of 50, 75 and 75 mg of ephedrine by mouth. The solid line indicates the blood pressure after the administration of 50 mg of ephedrine, the regularly broken line, after 75 mg, and the irregularly broken line, after 75 mg of ephedrine. The arrow indicates when ephedrine was given.

In seven patients with chronic hypotension to whom ephedrine was given regularly for from eight to thirty-seven days with an average of twenty days, the blood pressure was raised at all times of the day during the period of administration of ephedrine. The smallest increase in the average blood pressure was 4 mm systolic and 2 mm diastolic, and the greatest was 24 mm systolic and 9 mm diastolic with an average of 14.3 systolic and 5.3 diastolic for all cases. Details of the individual cases will be found in table 1. In none of these cases were there any objective signs of improvement besides elevation in blood pressure. As far as the subjective symptoms were concerned, three of the patients felt stronger, while four did not notice any change.

In the way of undesired effects, one patient had insomnia and another had marked palpitation for several hours after the administration of a single dose of ephedrine

On the whole, from our limited experience in the treatment of patients with chronic vascular hypotension with ephedrine, the conclusion can be drawn that the blood pressure level can be raised in these cases, and that about half of the patients feel subjectively stronger while taking the drug Miller,³ and Rowntree and Brown⁴ have

TABLE 1—*Blood Pressure of Patients with Hypotension During Ephedrine Therapy*

Case	Dose of Ephedrine	Time of Observation During Administration of Ephedrine in Days	Average Blood Pressure						Symptomatic Effects
			Before Administration of Ephedrine		After Administration of Ephedrine		Average Increase in Blood Pressure		
			Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	
39	25 mg in a m	19	99	60	111	68	15	8	Patient felt stronger and warmer while on ephedrine
40	50 mg three times a day	21	98	60	113	68	15	8	Patient was stronger, and felt warmth in feet which were usually cold, some insomnia
41	50 mg three times a day	22	96	70	107	67	11	-3	Patient felt better in general
42	50 mg three times a day	16	95	53	112	56	17	3	None
5*	50 mg four times a day	37	96	60	110	70	14	10	None
20*	50 mg three times a day	8	108	60	132	69	24	9	None
26*	50 mg three times a day	21	108	65	112	67	4	2	None

* Patient also had asthma

reported a maximum rise of from 10 to 50 mm in the systolic blood pressure and similar symptomatic results with ephedrine therapy in their cases of hypotension

Acute Hypotension of Shock—Chen⁵ was the first to try ephedrine in experimentally produced shock and hemorrhage in animals As a result of these experiments, he indicated in an early article the possibility

3 Miller, T G Ephedrine Its Use in the Treatment of Vascular Hypotension and Bronchial Asthma, *Ann Clin Med* 4 713, 1926

4 Rowntree, L G, and Brown, G E Ephedrine Therapy in Addison's Disease, *Endocrinology* 10 301, 1926

5 Chen (footnote 1, second reference)

of using it in similar conditions in man, and pointed out that theoretically ephedrine therapy can be successful only if hemorrhage is not excessive and when the patient is seen early. He also mentions the possibility of using the drug as a prophylactic agent before protracted operations.

We had the opportunity to use ephedrine in such conditions twice. In the first case, in which shock followed a postoperative hemorrhage in a man 80 years of age in whom the blood pressure had dropped from 185 systolic and 95 diastolic to 70 systolic and 30 diastolic, the patient was treated with 100 mg of ephedrine, three times a day, by mouth. The patient improved rapidly, and his blood pressure was up to its previous level two days after the administration of ephedrine was started. However, it is impossible to draw definite conclusions from this case, since with ephedrine the patient received a transfusion of blood and was given caffeine.

In the second case, one of surgical shock in a man, aged 58, in whom the blood pressure decreased from 110 systolic and 78 diastolic to 65 systolic and 0 diastolic, the patient was treated with ephedrine after transfusion of blood and medication with caffeine had failed to improve his condition. He received four doses of 100 mg of ephedrine at hourly intervals. An hour after the first dose, a reading of the blood pressure could not be obtained. An hour after the second and third doses the blood pressure was from 60 to 70 systolic and 0 diastolic. An hour after the fourth dose, the blood pressure was again unobtainable, and a little later the patient died. In this case ephedrine medication, used as a last resort, was probably begun too late to be of any benefit. In the literature, Miller⁶ and Chen and Schmidt⁶ reported several cases of surgical shock in which the patients were treated with ephedrine. In most of these cases, ephedrine therapy did not give beneficial results even when the drug was given intravenously. In a later paper, Chen and Schmidt⁷ expressed the opinion that ephedrine may be injurious to the heart, which is impaired in shock through a deficient coronary circulation. Rudolf and Graham⁸ have reported good results from ephedrine medication in early cases of acute hypotension following spinal anesthesia, and as a prophylactic before such anesthesia. The evidence accumulated to date concerning the value of ephedrine therapy in acute hypotension of shock forces one to conclude that its beneficial effect is doubtful, and that favorable results can be expected only if it is given early or as a prophylactic.

6 Chen and Schmidt (footnote 2, first reference)

7 Chen and Schmidt (footnote 2, second reference)

8 Rudolf, R. D., and Graham, J. D. Notes on Sulphate of Ephedrine, *Am J M Sc* **173** 399, 1927

ASTHMA AND HAY-FEVER

On the strength of Chen's⁶ demonstration of the capacity of ephedrine to produce relaxation of the bronchial musculature in experimental animals in which artificial spasms of the bronchi were induced by physostigmine, Miller⁹ gave the drug orally to several asthmatic patients in 1925 and obtained good results. Following the publication of this work, treatment with ephedrine was started in a series of patients at the University of California allergy clinic, including thirty patients with bronchial asthma, three patients with hay-fever and nine patients with both bronchial asthma and hay-fever, a total of forty-two cases. Our group of patients with hay-fever is small, owing to the fact that the present work with ephedrine was done between the months of August and March when practically all cases of hay-fever caused by pollen are quiescent. Only patients in the active stage of the two conditions were selected for ephedrine medication, and no other form of treatment was used in conjunction with this drug.

Clinical data concerning the individual cases which were deemed essential in the evaluation of the therapeutic results of ephedrine in each case, namely, the age of the patient, duration of the condition, frequency and severity of attacks, allergic status and previous treatment are summarized in table 2, together with the dose and method of administration of ephedrine, the symptomatic effects and the undesirable effects.

Asthma—In asthma, in addition to the foregoing data, determinations of the vital capacity were repeatedly made on nineteen patients, both before and after ephedrine therapy. The best vital capacity between attacks as compared to the theoretical normal vital capacity calculated for each patient according to Dreyer's work, "The Assessment of Physical Fitness," served to indicate the amount of permanent functional impairment of the lungs caused by asthma, and thus furnished an objective criterion concerning the severity of this condition in our patients as a group. The average vital capacity of our group was 81 per cent of the calculated normal. Patients with cardiac diseases were not included in this group. A still more useful application of measurements of vital capacity was found in objectively judging the severity of individual paroxysms of asthma and the degree of bronchial relaxation afforded by ephedrine and epinephrine. Finally, measurements of vital capacity were used as a check on the patient's statement in regard to symptomatic relief after the administration of ephedrine in an attack.

Ephedrine was given in doses of from 25 to 100 mg. The frequency of administration varied from one dose, as needed for paroxysms of asthma, to doses given four times a day. As a rule, the patients were

⁹ Miller, T. G. A Consideration of the Clinical Value of Ephedrine, *Am J M Sc* **170** 157, 1925.

TABLE 2—Clinical Data of Patients with Asthma and Hay-Fever

Case	Age	Clinical Diagnosis	Duration of Condition in Years	Frequency of Attacks	Severity of Attacks	Protein Sensitization	Previous Treatment	Ephedrine		Undesirable Effects	
								Dose	Method of Administration		
1	64	Asthma	8	Mild attacks daily, severe attacks from 3 to 4 times a week	+++	Negative	Epinephrine	25 to 50 mg as circumstances required	Oral	Complete relief	None
2	40	Asthma	3	Every few months for several days	++	Negative	Epinephrine	25 to 50 mg as circumstances required	Oral	Complete relief	None
3	54	Asthma	38	All year, from 4 to 5 attacks a day	+++	Positive	Potassium iodide, Shipman's powders	25 mg twice a day	Oral	Complete relief	Some nervousness, mild diuresis and constipation
4	27	Asthma	22	Weekly	++ to +++	Negative	Epinephrine calcium chloride 1 v, inhalations of stramonium, bact vaccine	50 mg three times a day 25 to 50 mg as circumstances required	Oral Hypo	Partial relief Complete relief	None
5	28	Asthma	27	Daily in winter	++	Negative	Epinephrine "Asthmador"	50 mg four times a day	Oral	Partial relief	None
6	21	Asthma	19	Daily	++ to +++	Negative	Epinephrine, bact vaccine, calcium chloride 1 v, sodium iodide	50 mg four times a day	Oral	Complete relief	None
7	53	Asthma and hay fever	2	Daily	++	Positive	Sodium iodide	50 mg three times a day	Oral	Complete relief	None
8	29	Asthma	6	Daily	++ to +++	Negative	Epinephrine, asthma cigarettes, bact vaccine, potassium iodide	3 per cent 50 mg three times a day	Nasal spray Oral	Partial relief	Nausea
9	26	Hay fever	4	Daily	++	Positive	Bact vaccine	50 mg three times a day	Oral	Partial relief	Nervousness, palpitation, insomnia
10	36	Asthma	7	Daily	+++	Negative	Epinephrine, potassium iodide	3 per cent 25 mg one dose	Nasal spray Oral	No relief	Marked palpitation all night
11	50	Asthma and hay fever	18 5	Daily	+++	Negative	Epinephrine, potassium iodide, belladonna cocaine	25 mg four times a day	Oral	No relief	Insomnia, nervousness, palpitation, nausea, vomiting
12	45	Asthma	6	Nightly	++	Negative	Epinephrine, belladonna, potassium iodide	25 to 50 mg at night	Oral	Complete relief	None

13	61	Asthma	15	Continuous	++	Epinephrine, potassium iodide	Oral	Complete relief	Slight nausea at times
14	23	Asthma and hay fever	7	Nightly	++	Potassium iodide	Oral	Partial relief	Marked nervousness and insomnia
15	43	Asthma and hay fever	All life	Several times a year, last attack 4 months continuous	+++	Epinephrine	Oral	Complete relief	None
16	52	Asthma	12	Nightly	++	Epinephrine, bicalcine, belladonna, potassium iodide	Oral	Partial relief	None
17	23	Asthma	11	Daily from 4 to 5 times	+++	Epinephrine four times a day, potassium iodide	Oral	Partial relief, (epinephrine only once a day)	None
18	34	Asthma	3	Daily	++	Epinephrine, potassium iodide	Oral	No relief	None
19	28	Hay-fever	3	Daily	+	None	Oral	Complete relief	None
20	66	Asthma	10	Nightly	++	?	Oral	Complete relief	None
21	25	Asthma and hay-fever	1	Daily	++	?	Oral	Partial relief	None
22	47	Asthma	10	Daily in winter	++		Oral	Complete relief	Some tremor
23	39	Asthma and hay-fever	23	Irregularly every months	+ to +++	Bacterial vaccine	Oral	Complete relief	None
24	54	Asthma	All life	Seasonal with cold weather	+ to +++	Epinephrine	Oral	Partial relief	None
25	56	Asthma	15	Continuous	+++	Belladonna, potassium iodide	Oral	Partial relief	None
26	51	Asthma	12	Every few weeks	++	Epinephrine	Oral	Complete relief	None
27	23	Asthma	21	From 1 to 2 times a month for from 1 to 3 days	++	Epinephrine	Oral	Complete relief	None
28	24	Asthma and hay-fever	14	Continuous, worse in winter	+ to +++		Oral	Complete relief	None
29	19	Asthma	15	Nightly	+++	Epinephrine	Oral	Complete relief	None

TABLE 2—Clinical Data of Patients with Asthma and Hay-Fever—Continued

Case	Age	Clinical Diagnosis	Duration of Condition in Years	Frequency of Attacks	Severity of Attacks	Protein Sensitization	Previous Treatment	Ephedrine			Undesirable Effects
								Dose	Method of Administration	Symptomatic Effects	
30	40	Asthma	1½	Continuous	+		Atropine, codeine	25 to 50 mg three times a day	Oral	Partial relief	None
31	16	Asthma and hay fever	32	Beginning at age of 14, for 2 years, 30, for 1 year, now for 3 months	+ to +++	Positive	Epinephrine	100 mg three times a day	Oral	Marked relief in attacks, no attacks if taken regularly	None
32	52	Asthma	6	Weekly to daily	+++	Negative	Epinephrine, iodide, morphine	50 mg as circumstances required	Oral	Complete relief	None
33	31	Asthma	8	Monthly for 1 week	++	Negative	"Rhine", "asthma serum"	25 mg three times a day	Oral	Partial relief	Some nervousness
34	22	Asthma	21	Every 2 to 3 months, now constant	+		Epinephrine	50 mg three times a day	Oral	Partial relief	None
35	73	Asthma	40	Beginning at age of 33, for 9 months, now daily for 2 years	+++		Epinephrine, potassium iodide	50 mg as circumstances required	Oral	Complete relief	None
36	30	Asthma	20	Daily	++	Negative	Epinephrine, potassium iodide	25 to 50 mg as circumstances required	Oral	Complete relief	Insomnia
37	34	Asthma	1½	Two to three days weekly	+	Positive		25 mg as circumstances required	Oral	Complete relief	None
38	30	Asthma	10	One week every month	+			25 mg as circumstances required	Oral	Partial relief	
		Hay-fever		All year round				3 per cent	Nasal spray	Complete relief	Fulness in head
46	59	Asthma	13	Nightly	++	Positive	Vaccine, sodium iodide, Tucker's remedy	50 mg at night	Oral	Partial relief	Insomnia all night
47	37	Asthma	1	One year ago, nightly for 2 months, now for 3 months nightly	+++	Positive	Epinephrine, belladonna, cigarettes	50 mg at night and as circumstances required	Oral	Complete relief	None
48	19	Asthma	13	Every 2 days to 2 weeks, lasting 1 hour to 4 days	+++	Positive	"Asthmadore", belladonna, epinephrine	50 to 100 mg as circumstances required	Oral	Marked relief	None
49	16	Hay fever	13	All year round	++	Positive		3 per cent	Nasal spray	Marked relief	None

accorded great freedom in adjusting the dose and frequency of administration. In all but three patients, the drug was given orally. In three cases, ephedrine was given hypodermically during attacks of asthma for purposes of comparison, and in only one case was this method adopted as a routine procedure for severe attacks. This was done because the patient was getting only partial relief when the drug was taken orally, while he obtained complete relief with subcutaneous administration, at the same time, the unpleasant effects of epinephrine were obviated.

The therapeutic effects of ephedrine were classified in the table under the headings of "complete relief," "marked to partial relief" and "no relief" on a subjective-symptomatic basis, since our experience dealt with clinic patients in whom only occasional paroxysms of asthma were observed by one of us. We feel satisfied that the reports of "complete relief" by the patients are reliable, because over three fourths of our patients who gave this response had had previous injections of epinephrine for asthma and therefore presumably knew what "complete relief" meant. The other two headings are self-explanatory. Of thirty-nine patients with bronchial asthma, twenty-one (or 54 per cent) obtained complete relief from their paroxysms when ephedrine was taken after the onset of the paroxysm, and continued administration of the drug usually greatly reduced the number of attacks or prevented them altogether. Marked to partial relief was obtained by fifteen (or 38 per cent) of our patients. When ephedrine was taken regularly in this group, it often prevented the paroxysms, although after onset an attack could not be controlled completely by it. Three patients did not obtain benefit from ephedrine medication.

On careful analysis of the clinical data in our series of cases of asthma, it was found that the age and sex of the patients, the duration of the condition, the frequency and severity of the attacks, the coexistence of hay-fever and the allergic status did not play an important rôle in the degree of success with ephedrine therapy.

The only factor that had some influence in this sense was the previous treatment received by the patient for asthma, as most of the marked untoward symptoms necessitating the withdrawal of ephedrine in spite of the relief of asthmatic symptoms by the drug occurred in patients in whom the administration of epinephrine had been stopped immediately preceding ephedrine medication.

In table 3 we have compiled the results of ephedrine therapy in cases of asthma and hay-fever as reported in the English and foreign literature to date, making a total of over 330 cases. A comparison of results given by various writers shows that the percentage of successes, partial successes and failures is much the same in all series.

In our experience, symptomatic relief from oral administration of ephedrine was obtained in from five to thirty minutes. The following

TABLE 3—*Our Results with Ephedrine Therapy in Bronchial Asthma and Hay-Fever with a Summary of Results in the Literature to Date*

	Asthma				Hay Fever			Undesirable Effects		
	No of Cases	Complete Relief	Partial Relief	No Relief	No of Cases	Complete Relief	Partial Relief	None	Slight	Marked
Present report	39	21	13	3	12	7	1	29	7	6
Mullen (Am J M Sc 170 157, 1925)	7	1	2	1						
Miller (Ann Clin Med 1 713, 1926)	36	26	1	6						
Middleton and Chen (Arch Int Med 39 385 [Mch] 1927)	25	9	8	8						
Kammerer and Dorrei (Munchen med Wehnschr 73 1739, 1926)	8	4	3	1						
Pollak and Rabitschek (Wien Klin Wehnschr 59 753, 1926)	16	11	2	0						
Jansen (Klin Wehnschr 5 2102, 1926)	Not given	"Same results as Pollak and Rabitschek"								
Hess (Munchen med Wehnschr 73 1691, 1926)	15	"Some"	"Some"	"Rare cases"						
Thomas (Am J M Sc 171 719, 1926)	20	Relief 17		3						
Wearn (J A M A 57 833 [Sept 11] 1926)	6	6		0						
Rudolf and Graham (Am J M Sc 173 399, 1927)	2	1		1						
McDermot (Canad M A J 16 122, 1926)	20	"In most cases"								
Balyent (J Oklahoma M A 20 3 [Jan] 1927)	"More than 100"	"Of considerable value in at least 65%"		20%	Not given	Relief sometimes for a few minutes	20%			
						"Good Results" 13	"Full Results" 5			
Gaarde (Am J M Sc 172 588, 1926)					26		8			

Occasionally

Not mentioned

Not mentioned

Some patients

2

2%

Most patients

case (no 2) may serve as an illustration. The patient came to the clinic during an attack of asthma, with the vital capacity reduced from the usual 53 per cent of normal to 20 per cent and a blood pressure of 115 systolic and 90 diastolic. Fifty milligrams of ephedrine were given by mouth. Five minutes later, the patient had obtained complete symptomatic relief, her vital capacity was increased to 30 per cent of normal (or by 50 per cent), and her blood pressure was 130 systolic and 95 diastolic. Fifteen minutes after taking the drug, her vital capacity was 33 per cent of normal, and her blood pressure was 135 systolic and 95 diastolic. Such prompt action of ephedrine given orally, which has already been reported by McDermot, would almost make one look for a psychic explanation if it were not for the fact that complete symptomatic relief was accompanied by marked increase in the vital capacity and a considerable elevation in the blood pressure, which indicates that the action of the drug was responsible for all of these changes (charts 4 and 5).

Hypodermic administration of ephedrine during acute attacks of asthma in two of our patients took full effect in one and one-half and ten minutes, respectively). The first of these patients (no 27) obtained complete symptomatic relief one and one-half minutes following a hypodermic administration of 50 mg of ephedrine, while the blood pressure increased from 118 systolic and 78 diastolic to 130 systolic and 78 diastolic in five minutes and remained at this level. The second patient (no 31), who on previous occasions obtained marked but not complete relief from oral administration of ephedrine, was seen during an attack of asthma when the vital capacity was reduced from 89 per cent of normal to 32 per cent, and the blood pressure was 125 systolic and 97 diastolic. He was given 100 mg of ephedrine hypodermically in view of his weight (184 pounds), and ten minutes later had obtained his maximum but not complete relief from the drug. The vital capacity at that time had increased to 40 per cent of normal (or an increase of 25 per cent), and the blood pressure had risen to 130 systolic and 98 diastolic. Fifteen minutes after the first dose the patient received another injection of 100 mg of ephedrine, which in ten minutes raised the blood pressure to 136 systolic and 97 diastolic, but failed to give complete symptomatic relief or to increase the vital capacity. The condition of this patient remained the same for over an hour, when an injection of $\frac{1}{150}$ grains (0.0004 Gm) of atropine completely relieved the residual symptoms (charts 4 and 5).

At another time the same patient was seen in a more severe attack of asthma, which reduced his vital capacity to 12 per cent of normal, the blood pressure being 132 systolic and 100 diastolic. This time an injection of 0.5 cc of 1:1,000 solution of epinephrine was given to compare

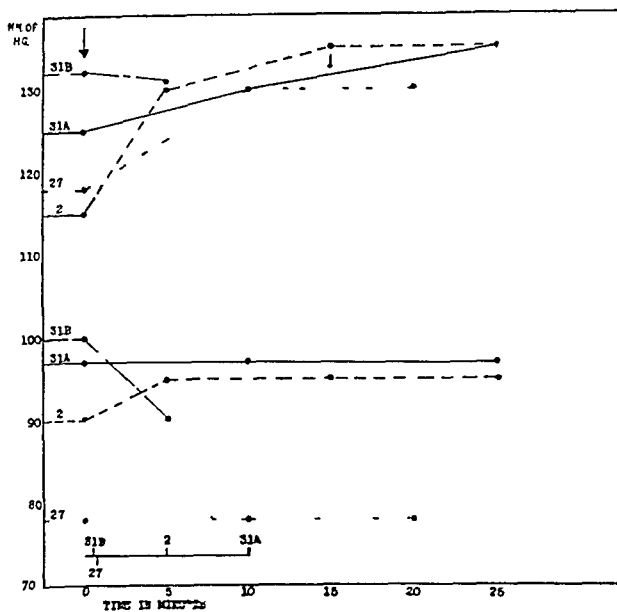


Chart 4—Curves showing blood pressure of three asthmatic patients after the administration of ephedrine and epinephrine during an attack. Number 2 indicates the curve for patient number 2 (weight 120 pounds) after the administration of 50 mg of ephedrine by mouth, number 27 indicates the curve for patient number 27 (weight 166 pounds) after 50 mg of ephedrine hypodermically, number 31A indicates the curve for patient number 31 (weight 184 pounds) after 100 mg of ephedrine hypodermically repeated after fifteen minutes, and number 31B indicates the curve for the same patient after the administration of 0.5 cc of epinephrine hypodermically during another attack. The lowest curve indicates the time of disappearance of symptoms for each patient. The arrow indicates when ephedrine was given.

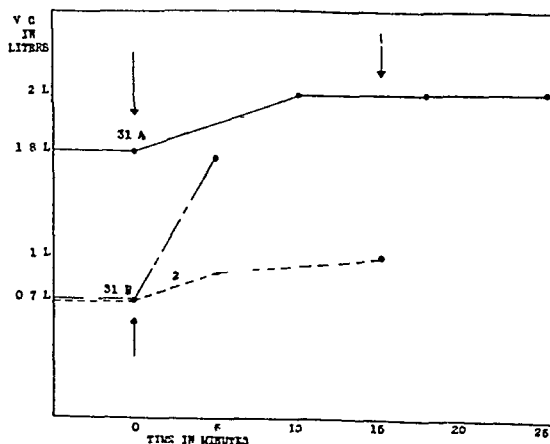


Chart 5—Curves showing vital capacity of two asthmatic patients after administration of ephedrine and epinephrine during attacks. Number 2 indicates the vital capacity for patient number 2 (between attacks 1.6 liters) during an attack and after the administration of 50 mg of ephedrine by mouth, number 31A indicates the vital capacity for patient number 31 (between attacks 4.4 liters) during an attack after the administration of 100 mg of ephedrine hypodermically repeated after fifteen minutes, and number 31B indicates the vital capacity of the same patient in another attack and after the administration of 0.5 cc of epinephrine hypodermically.

its action with that of ephedrine. After the injection of epinephrine the patient obtained complete symptomatic relief in about one minute with an increase in the vital capacity to 40 per cent of normal (or by 333 per cent) and a blood pressure of 130 systolic and 90 diastolic five minutes after the injection was given (charts 4 and 5).

These two cases serve well to illustrate that the action of ephedrine given by injection is generally more prompt than when the drug is given orally, but that it is slower than the action of epinephrine. The last case is also a good demonstration of the fact that epinephrine will give complete symptomatic relief when ephedrine fails to do so. This case also verifies the impression of all who have used ephedrine in the treatment of patients with asthma that it brings about a greater amount of bronchial relaxation, though the exact extent of this cannot be ascertained until patients with asthmatic attacks of the same severity, as shown by the decrease in vital capacity, have been treated with both drugs on different occasions.

Several writers who have had experience with ephedrine therapy recommend combining ephedrine with epinephrine for patients with asthma who are not relieved by ephedrine alone. In the few cases in which we have tried such a combination, severe nausea and vomiting occurred. Only one patient benefited temporarily by the combination of these two drugs, as ephedrine medication by mouth reduced the number of daily injections of epinephrine from four to one, but eventually he developed nausea and vomiting and had to discontinue the practice. As further evidence of an apparent incompatibility of ephedrine and epinephrine can be cited the fact already mentioned that most of our patients in whom marked undesirable effects of ephedrine supervened were receiving epinephrine up to the time when they were started on ephedrine. In this connection it is interesting to recall that Chen¹⁰ has shown by animal experiments that ephedrine and epinephrine have a synergistic action. Therefore, the possibility must be considered that marked untoward symptoms in these cases were due to synergism of the two drugs, in other words, that these patients were really getting an overdose. A rather dramatic incident pointing in that direction occurred to one of our patients to whom 0.8 cc. of a 1:1,000 solution of epinephrine was given for an attack of asthma which was partially relieved by 100 mg. of ephedrine taken twelve hours before the injection of epinephrine. Immediately after the injection, the patient complained of a severe suboccipital pain, the onset of which was simultaneous with a complete disappearance of asthmatic symptoms. The blood pressure, which was 150 systolic and 104 diastolic just before the injection, rose in one minute to 240 systolic and 110 diastolic, and it took two inhala-

10 Chen (footnote 1, fifth reference)

tions of amyl nitrite and two doses of $\frac{1}{100}$ grains (0.00065 Gm) of nitroglycerin to bring it down to its previous level after a period of forty minutes. A decision on this question can be arrived at after it is seen whether smaller doses of ephedrine and epinephrine given in conjunction will produce sufficient bronchial relaxation to relieve an asthmatic attack without causing excessive undesirable effects.

While ephedrine markedly increases the vital capacity during an acute attack of asthma, it does not seem to bring about permanent improvement of the functional capacity of the lungs, as a comparison of readings of the vital capacity between attacks before and after ephedrine therapy indicates. We obtained an average increase of 0.2 liters in all patients with asthma who were given ephedrine in whom such readings were taken, which, of course, is negligible in view of the considerable fluctuations of the readings of the vital capacity from day to day in asthmatic subjects. This observation is not astonishing if it is remembered that the permanent reduction of vital capacity in asthmatic subjects is produced by emphysema for which the asthma is responsible but not by the asthma per se.

The only type of asthma in which ephedrine theoretically would be able to effect an increase of the vital capacity between acute attacks is one in which the patient is having a mild spasm of the bronchioles all of the time, with exacerbations of this spasm in the form of acute attacks. An illustration of such a case is furnished by the patient in case 3, and the results obtained with ephedrine therapy over a period of six months are given in chart 6. When the patient came to the clinic, attacks of asthma were continuous day and night, with from four to five severe attacks every twenty-four hours. She was given a dose of from 25 to 50 mg of ephedrine three times a day and as circumstances required. The drug completely controlled the individual attacks of asthma but unfortunately caused a number of undesirable symptoms, namely, nervousness, palpitation, constipation, diuresis and marked insomnia if taken at night. After experimenting for several days, it was found that the patient obtained the greatest comfort with the least amount of undesirable symptoms when given 25 mg of ephedrine twice a day (after breakfast and after lunch), she has been on this dosage for the last six months. Knowing that we were interested in the results of ephedrine therapy, the patient expressed her gratitude to us by keeping a daily record of her attacks, which we have reproduced in chart 6. The chart shows not only abrupt diminution of the number of attacks a week after ephedrine therapy was started, but also a more gradual diminution of the frequency of attacks during the six months while the patient was being treated with ephedrine. Three months after the beginning of the administration of ephedrine, when determinations of vital capacity were started, the vital capacity was 54 per cent of normal. The patient's lung capacity

gradually increased under treatment, until two months later it had reached 100 per cent, it has remained at practically the same level. Such marked improvement cannot be explained on the basis of seasonal variations, since it occurred during the months of November and December, when California has its rainy season.

We feel that a few words should be said in regard to the blood pressure in asthmatic patients who are receiving ephedrine, because our observations in this regard differ materially from those of other workers who have made statements to the effect that the blood pressure is little affected in these cases. Chen⁷ explains this lack of rise in the blood pressure by differences in the pulmonary circulation.

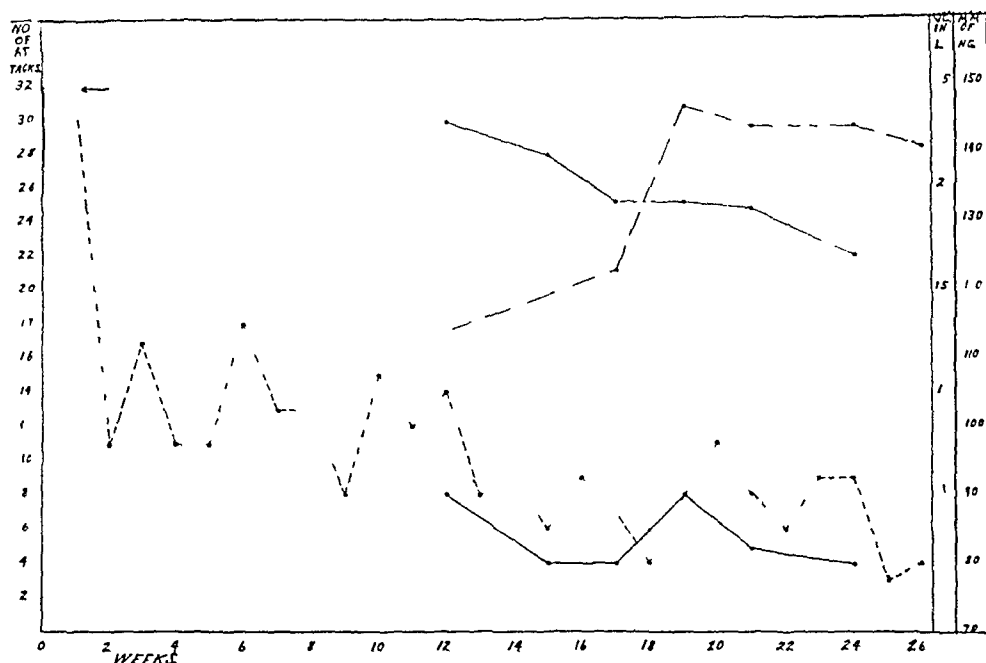


Chart 6—Chart showing blood pressure, vital capacity and number of weekly attacks of asthma in patient number 3 (weight 98 pounds) who was given 25 mg of ephedrine by mouth twice daily for six months. The regularly broken line indicates the number of attacks a week, the irregularly broken line, the vital capacity, and the unbroken line, the systolic and diastolic blood pressure. The arrow indicates when the administration of ephedrine was started.

On the contrary, it has been our experience to observe rises in blood pressure in asthmatic patients that in no way differed in degree, time of onset or duration from those in patients free from asthma. This applies to blood pressure curves obtained after single doses of ephedrine, as can be seen in the three curves in chart 4, and also to the more constant increase in the blood pressure level produced by the regular administration of ephedrine. As can be learned by glancing at table 1, the average increase in blood pressure in three patients with asthma, who also had hypotension, was 14 mm systolic and 7 mm diastolic as against an

average increase of 14.5 mm systolic and 4 mm diastolic in four patients with hypotension who were free from asthma.

A notable exception to this rule, which we found to be true in all cases in which systematic estimations of the blood pressure were carried out, is presented in case 3, in the course of the last four months on ephedrine therapy, the blood pressure of this patient decreased from 146 systolic and 90 diastolic to 135 systolic and 80 diastolic (chart 6). We feel that more observations over a longer period of time on this and other patients are required before a definite opinion can be formulated, but the possibility of a parallel between this case, in which prolonged administration of ephedrine was carried out, and cases in which marked hypotension bordering on Addison's disease developed after long continued medication with epinephrine, must be kept in mind.

Hay-Fever.—The dosage and frequency of administration of ephedrine for hay-fever was the same as for asthma. With one exception, the drug was given at first by mouth, in two cases, oral administration was later supplemented by a 3 per cent nasal spray in order to obtain complete relief. In one case, oral administration was replaced by the spray to obviate marked untoward symptoms. One patient was given ephedrine only by the nasal spray. In none of these cases was the nasal mucosa irritated as so often happens after the administration of epinephrine. The results of ephedrine therapy were classified under the same headings as those of asthma. Of twelve cases of hay-fever, complete relief was obtained in seven (or 58 per cent), marked to partial relief was given by the drug in four cases (or 33 per cent), and complete failure occurred in one instance.

As can be seen from table 3, our experience with ephedrine in hay-fever is in fairly close agreement with that of Gaarde,¹¹ and differs from that reported by Balyeat,¹² who sometimes obtained only transient relief from symptoms in his cases of hay-fever.

Untoward Effects.—Disagreeable effects from ephedrine medication in the form of nausea, nervousness, insomnia, palpitation and, rarely, constipation and diuresis were met with in 30 per cent of our cases, and in 12 per cent these were so severe that the administration of the drug had to be discontinued. The undesirable effects met with in the treatment of patients with asthma and hay-fever are classified in table 3 according to the degree of severity, as are also the disagreeable symptoms reported in the literature whenever any statements regarding them were made. As pointed out before, the most severe untoward symptoms that

11 Gaarde, F. W., and Maytum, C. K. The Treatment of Hay-Fever with Ephedrine, *Am J M Sc* **172**: 588, 1926.

12 Balyeat, R. M. Use of Ephedrine in Asthma and Hay-Fever, *J Okla-homa M A* **20**: 3 (Jan) 1927.

we noted occurred in patients who received epinephrine up to the day when they were given ephedrine. It is possible that by combining sedatives with ephedrine medication many of the undesirable effects of this drug can be eliminated or at least considerably lessened.

To investigate the effects of the repeated administration of ephedrine, Chen¹³ gave this drug in daily doses for a month to a number of rabbits and white rats, and reported no pathologic changes at autopsy in any organs in these animals. With a view of determining whether any possible renal changes take place in man, we began to analyze the urine before and after ephedrine medication. Although we have not done this in a sufficient number of cases and have not followed our cases in this respect long enough, it may be well to mention in a preliminary way that in a group of fifteen patients, several showed red blood cells or casts in the urine after being given ephedrine therapy for a short time. These observations show that the question of renal irritation from ephedrine seems to be one worthy of investigation. In this connection, a recent article by Starr¹⁴ deserves mention. He discusses the production of transient albuminuria caused by renal vasoconstriction after the administration of ephedrine, and makes a statement to the effect that he obtained evidence showing that ephedrine is not intrinsically injurious to the kidney, unfortunately, the nature of this evidence is not given. Rudolf and Graham⁸ also do not report signs of renal irritation in ten of their cases.

Tolerance—The question of tolerance to ephedrine is interesting because of the great similarity of this drug to epinephrine, repeated administrations of which result in a certain tolerance. Evidence obtained by Chen¹³ from experiments on animals tends to show that tolerance does not develop after repeated administrations of ephedrine for a month. On the other hand, in five patients in our series of cases of asthma and hay-fever, or in fully 15 per cent of the patients to whom ephedrine was given over any length of time, the beneficial effects of ephedrine have suffered considerable diminution in the course of time, and in four patients in whom complete relief was obtained at first, only partial relief was reported later, while in one patient in whom partial relief was afforded at first, the drug ceased to give any relief after a short time. In addition, two of our patients showed acquired tolerance to ephedrine by reporting the disappearance of the nausea which at first accompanied the taking of the drug. In reporting his series of asthma

13 Chen (footnote 1, third reference)

14 Starr, I, Jr. The Production of Albuminuria by Renal Vasoconstriction in Animals and in Man, *J. Exper. Med.* **43** 31, 1926

cases in which the patients were treated with ephedrine, Balyeat¹² also comments on the fact that in some cases the continued use of the drug causes unpleasant effects to disappear. The same experience is related by Kammerer¹⁵ in his paper.

OTHER CONDITIONS

Toxic Erythema—Spectacular results were obtained in a case of extensive toxic erythema accompanied by pruritus, as five minutes after the patient had taken 65 mg of ephedrine by mouth, the erythema disappeared, and the itching ceased. The erythema recurred on the next day over a limited area, but again promptly disappeared after the same dosage of ephedrine.

Urticaria—Ephedrine was given to seven patients with urticaria. In five of these cases, no improvement was noted either in the appearance of the rash or in the intensity of subjective symptoms. In two patients, definite improvement was observed, but the time which elapsed between the beginning of ephedrine therapy and the relief from urticaria was compatible with spontaneous recovery.

Two of the patients who failed to improve after the administration of ephedrine were given one injection of epinephrine each, and in one of them considerable improvement was noted shortly after the injection.

Miller⁹ is the only author who has used ephedrine in urticaria and reported his results in two cases, in one subjective relief and in the other disappearance of the rash were observed following administration of this drug.

Angioneurotic Edema—Three patients with angioneurotic edema failed to react favorably to the administration of ephedrine. One of these patients improved markedly after two injections of epinephrine. Following the injections, this patient was treated with ephedrine, and the edema did not recur.

SUMMARY

Hypotension—Chronic Hypotension. Ephedrine, usually in doses of 50 mg, three times a day, was given to a number of patients who had hypotension, this was followed by a maximum increase in the systolic blood pressure of between 9 and 46 mm and a sustained average elevation in the systolic blood pressure of 14.3 mm. We observed the same increase in the systolic blood pressure in patients with normal blood pressure and in those affected by asthma. The diastolic pressure varied between -10 mm and $+10$ mm, with some rise in most cases. It appears that the amount of rise in the systolic blood pressure is inde-

15 Kammerer, H., and Dorrer, R. Kunze Mitteilung über die Wirkung des Ephedrine-Merck auf Asthmakranke, München med Wchnschr 73 1739, 1926.

pendent of the weight of the patient, but is constant in the same patient and within certain limits roughly proportionate to the dose of ephedrine

Repeated administrations of ephedrine, besides increasing the blood pressure level in these patients, imparted to some of them a feeling of strength and well-being

Acute Hypotension Ephedrine was given to two patients in a state of surgical shock. In one case the patient recovered, but, since at the same time transfusion of blood and caffeine medication were given, it is hard to tell how much was accomplished by ephedrine. The other patient died.

Asthma and Hay-Fever—Thirty-nine patients with asthma and twelve patients with hay-fever were treated with ephedrine, which served to control the attacks and, when used constantly, to prevent them in many instances. Ephedrine therapy gave complete relief in 56 per cent and partial relief in an additional 24 per cent of our cases. In 8 per cent of the cases, failures were due to absence of relief, and in 12 per cent of the cases to marked untoward symptoms.

Oral administration gave relief in our cases in from five to thirty minutes, and hypodermic administration acted more promptly. Compared to epinephrine, ephedrine acted more slowly and less completely, the action, however, continued much longer, and in most cases the disagreeable by-effects of epinephrine were avoided. Combination of these two drugs in our experience often produced marked untoward symptoms.

Undesirable effects from ephedrine medication in the form of nausea, vomiting, nervousness, insomnia and palpitation were encountered in 30 per cent of our cases, and in 12 per cent of the cases these symptoms were so severe that the administration of the drug had to be discontinued. Some degree of tolerance to ephedrine was obtained in at least 15 per cent of our patients.

Other Conditions—In one case of toxic erythema, spectacular recovery was obtained with ephedrine. In seven cases of urticaria, the benefit from ephedrine therapy was doubtful in two and absent in five. Three patients with angioneurotic edema failed to improve after the administration of ephedrine.

CONCLUSIONS

- 1 Ephedrine may be of benefit in some cases of chronic hypotension.
- 2 The results of ephedrine therapy in acute hypotension of shock are doubtful.
- 3 In asthma and hay-fever, ephedrine is of great value, completely controlling attacks in about half of the cases and giving partial relief in another one fourth of the cases.
- 4 The advantage of ephedrine over epinephrine are that it is effective when given by mouth, that its action is longer, that it does not pro-

duce local irritation when given as a nasal spray, and that in most cases undesirable symptoms, such as tremor and palpitation, do not occur as with epinephrine

5 Among the disadvantages of ephedrine are (a) failure at times to relieve asthmatic attacks when epinephrine is effective and (b) in occasional cases, untoward symptoms which are more marked than those following the administration of epinephrine

6 The use of ephedrine in urticaria and angioneurotic edema is not promising

MYCOTIC GASTRITIS¹

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CHICAGO

Since the thrush organism is found in the mouths of a large proportion of normal persons (Merke,¹ 35 per cent, Brunstein,² 40 per cent), and gastric conditions are particularly favorable for the growth of the various molds (Askanazy³), it is not surprising to learn that the normal stomach quite frequently harbors fungi. Although Kirch and Stahnke⁴ were unable to demonstrate the presence of molds in the aspirated contents of the stomach in any of thirty cases, the positive observations obtained by others (Moppert and Kagen,⁵ Cafasso⁶ and Hartwich⁷) are sufficiently conclusive to indicate that the occurrence of fungi in the intact stomach, if not universal, is at least widespread. The observation of molds in twenty of thirty-two normal stomachs viewed by Crasset⁸ at postmortem examinations in cases in which contamination from the pharynx and esophagus was eliminated lends further support to this view. On the basis of available evidence, it can be safely assumed that when fungi are present in the intact stomach, they play little if any rôle in the production of gastric disease. In fact, the frequency with which these organisms are found in stomachs of normal persons has led to the assumption that they represent harmless saprophytes. The symptoms attributed in the older literature, especially before the advent of the roentgen ray, to molds which were found in the aspirated contents

¹ From the Departments of Medicine and Pathology of the University of Illinois College of Medicine.

1 Merke, F. Ueber die Bedeutung des Soorpilzes bei dem chronischen Magengeschwür, *Beitr z klin Chir* **130** 549, 1924.

2 Brunstein, A. L'oidium albicans dans la bouche des personnes saines, *These*, Geneva, 1907.

3 Askanazy, M. Ueber Bau und Entstehung des chronischen Magengeschwürs sowie Soorpilzbefunde in ihm, *Virchows Arch f path Anat* **250**:370, 1924.

4 Kirch, E., and Stahnke, E. Pathologisch-anatomische, klinische, und tierexperimentelle Untersuchungen über die Bedeutung des Soorpilzes bei dem chronischen Magengeschwür, *Mitt a d Grenzgeb d Med u Chir* **36** 174, 1923.

5 Moppert, G. G., and Kagen, G. Recherches sur la presence de muguet (oidium) dans le liquide gastrique d'individus normaux et d'individus atteints d'ulcere et de cancer de l'estomac, *Rev med de la Suisse Rom* **42** 505, 1922.

6 Cafasso, K. Ueber das Vorkommen des Soorpilzes im Magensaft bei Ulkus und bei anderen Erkrankungen des Magens, *Med Klin* **18** 828, 1922.

7 Hartwich, A. Ueber das Vorkommen von Soor im chronischen Magengeschwür, in hamorrhagischen Erosionen und Magencarcinomen, *Virchows Arch f path Anat* **241** 116, 1923.

8 Crasset, referred to by Askanazy (footnote 3, p. 456).

of the stomach in all probability were due to undiscovered independent gastric lesions

Although it is generally agreed that the presence of fungi *per se* in the intact stomach does not lead to ill effects, opinions concerning the rôle of these parasites when associated with a gastric lesion vary widely. The presence of fungi in the walls of the chronic round ulcer of the stomach, an observation made by Heller⁹ in 1895, received little attention until the appearance of Askanazy's¹⁰ work in 1921. Askanazy was able to demonstrate the presence of fungi in more than one half of his series of cases of ulcer, and he ascribed to these organisms a rôle in the maintenance of the chronicity of the lesions.¹ Notwithstanding the fact that some investigators have failed to demonstrate the presence of molds culturally or histologically in a large proportion of the chronic ulcers they have examined, Askanazy's work has received sufficient confirmation to justify the assumption that chronic ulcers quite frequently harbor mycotic organisms. Whether a relationship of cause and effect exists between the failure of an ulcer to heal and the fungi found in its base or walls is still a matter of controversy.

On the basis of extensive and well controlled investigation, Askanazy was led to assume in his first work¹⁰ that the fungus did not represent an unimportant saprophyte when found in connection with an ulcer, the state of which would be identical whether the fungus was present or not. In a subsequent report,³ this author gives the following reasons for believing that the mycotic organisms are of pathologic significance: their exceedingly frequent occurrence in freshly resected ulcers, the frequent correspondence in location of the fungi and the inflammatory reaction, the often intracellular location of the parasites, repeated invasion of the granulation tissue zone by the mycelia, apparent extension of the filaments into the blood vessels and even through the entire thickness of the gastric wall. Support is lent Askanazy by the observations and opinions of von Meyenburg,¹¹ Cafasso,⁶ Hartwich,⁷ de Vecchi¹² and Merke.¹ On the other hand, Nissen,¹³ Aschoff,¹⁴

9 Heller, A. Beitrag zur Lehre vom Soor, *Deutsches Arch f klin Med* **55** 116, 1895

10 Askanazy, M. Ueber Bau und Entstehung des chronischen Magengeschwurs sowie Soorpilzbefunde in ihm, *Virchows Arch f path Anat* **234** 111, 1921

11 Von Meyenburg, H. Ueber Schimmelpilzkrankungen der Magenwand, *Frankfurt Ztschr f Path* **23** 86, 1920

12 De Vecchi, referred to by Askanazy (footnote 3, p 462)

13 Nissen. Ueber die Bedeutung des Soorpilzes für das chronische Magengeschwür, *Verhandl d deutsch path Gesellsch* **18** 283, 1921

14 Aschoff, L. Aussprache zu Nissen, *Verhandl d deutsch path Gesellsch* **18** 287, 1921

Steinberg,¹⁵ Frank,¹⁶ and Kirch and Stahnke¹ in their respective considerations of the subject attached little if any significance to the presence of fungi in the genesis or maintenance of the chronicity of peptic ulcer. The arguments pro and con were well summarized by Hauser,¹⁷ who arrived at the conclusion that the presence of a fungous growth on the floor or margins of an ulcer may have some tendency to inhibit its healing. One should, he stated, assume, however, that this inhibitory effect is of minor importance as compared to the influence of other factors.

In addition to the group of patients with normal stomachs, in which the rôle of the fungus is admittedly an insignificant one, and the group with a simple ulcer, in which the importance of the mold is questionable, there is a third group in which characteristic pathologic lesions are produced, due directly to the effect of the fungi present. The last group includes patients with true mycotic gastritis, of which little or no mention is made in American or English literature. Einhorn,¹⁸ Knapp¹⁹ and Kellogg²⁰ dealt with the subject of fungi in aspirated gastric contents, but they did not refer to actual mycotic infection of the stomach. Careful search of the literature has failed to disclose any reports of mycosis of the stomach occurring in this country or in England. Therefore, a rather detailed report of the following case of mycotic gastritis appears warranted.

REPORT OF CASE

History—H. R., a white man, aged 27, a chauffeur, on March 26, 1926, was admitted to the Women's and Children's Hospital in Chicago in the service of Dr. P. M. Stetler, who kindly furnished the following clinical account.

On admission the patient complained of persistent vomiting, weakness and occasional oozing of blood from the mouth and nose. He stated that three weeks prior to entrance, he had had an attack of grip which lasted two weeks and which was accompanied by infrequent nose bleeds. A week prior to entrance, he returned to work, and, on the following day, he was suddenly seized by severe epistaxis while driving his taxicab. He was taken to the Cook County Hospital, where a posterior nasal packing was introduced and horse serum administered. The following day, March 22, he returned home, and since that time he had been able to retain little food or water on account of vomiting. Blood was not seen in the emesis, nor was abdominal pain present at any time. In addition to

15 Sternberg, C. Aussprache zu Nissen, Verhandl. d. deutsch. path. Gesellsch. **18** 286, 1921.

16 Frank, P. S. Ueber die Beziehungen des Soorpilzes zu dem runden Magengeschwür, Wien Arch. f. inn. Med. **5** 39, 1922.

17 Hauser, G. Infektiose und infektios-toxische Einflüsse in Henke, F., und Lubarsch, O. Handbuch der speziellen Pathologischen Anatomie und Histologie, Berlin, 1926, vol. 4, p. 736.

18 Einhorn, M. The Occurrence of Moulds in the Stomach and its Probable Significance, M. Rec. **57** 1025, 1900.

19 Knapp, M. I. Gastrosia Fungosa, Am. Med. **10** 56, 1903.

20 Kellogg, J. H. Moulds in the Stomach, M. News **77** 88, 1900.

the vomiting, since March 22 he had suffered from slight but daily oozing of blood from the inside of the left cheek and occasionally from nose bleeds

With the exception of the resection of a rib undertaken for empyema five years previously and an accident seven months before admission, noteworthy information was not obtained from the past history. The accident which occurred July 17, 1925, was apparently severe, the patient was thrown against the steering wheel of his taxicab with such force that the wheel was broken. He suffered particularly from injuries to the arms and legs, on account of which he was unable to work for approximately four months. Following eating during this period, he had occasional attacks of vomiting which usually occurred in the forenoon. The attacks lasted only a few hours after which the patient was able to eat with little discomfort. In the family history, it was noted that the patient's mother had died of cancer of the stomach at the age of 35, and that two sisters had succumbed to tuberculosis.

Physical and Laboratory Examinations—Physical examination disclosed a young man about 30 years of age, thin, but not emaciated, who appeared to be quite ill. The temperature, pulse and respiratory rates were normal. The essential changes consisted of a small ulceration on the anterior portion of the left side of the nasal septum covered with a gray exudate and a similar area on the inside of the left cheek opposite the last lower molar. There was physical evidence of a thickened pleura over the base of the left lung at the site of an old rib resection. The heart was slightly enlarged, and the second aortic tone accentuated. The blood pressure measured 140 mm systolic and 90 mm diastolic.

The urine had a specific gravity of 1.029 and contained albumin (++) and a few red cells, but no casts. The hemoglobin determination was 40 per cent, the red cell count 2,600,000 and the white cell count 10,600, 86 per cent of which were polymorphonuclears.

Subsequent Course and Treatment—On the morning of entrance, the patient vomited undigested food but no blood. Nothing was given by mouth for forty-eight hours, fluids being supplied by hypodermoclysis and proctoclysis. Efforts to control the hemorrhage from the mouth and nose by chemical and actual cauterization proved futile, and a posterior nasal packing was required. The vomiting ceased for twenty-four hours, during which time the patient appeared to be improved. On the second day after entrance, a gastric lavage yielded an old blood clot (swallowed?) but no recent hemorrhage. The following day, the patient vomited clotted blood and a small amount of bright red fluid. On March 30, four days after admission, 500 cc of blood was introduced into the patient's veins, following which he rallied, accordingly, another transfusion was performed on April 5. The patient appeared to improve until April 10, sixteen days following admission, that day, he vomited bright red blood approximately every hour. The emesis continued for a period of twenty-four hours, and then practically ceased. The erythrocyte count dropped to 900,000, and on April 12 a third transfusion was undertaken. Improvement in the blood picture occurred rapidly, the hemoglobin rising from 10 per cent to 45 per cent (recorded the day before death), following a fourth transfusion, while the red blood count increased to 2,000,000. On April 15, the temperature, which previously was below 100 F, had risen to 102 F. Later in the course of illness, physical symptoms of consolidation were elicited over the upper part of the right side of the chest, and a diagnosis of pneumonia was made. The patient became more and more toxic, and died on April 20, 1926.

Autopsy—The postmortem examination was performed by Dr. R. H. Jaffe, whose anatomic diagnosis was lobar pneumonia of the right upper and middle

lobes (gray hepatization) high grade chronic diffuse nephritis (secondary contracted kidneys), moderate anemia, localized mycotic gastritis, moderate hypertrophy of the left ventricular myocardium, edema of the lungs, hypostatic pulmonary hyperemia petechial hemorrhages of the omentum, localized fibrous perihepatitis fibrous pericholecystitis slight bilateral hydronephrosis, and hemosiderosis of the liver

Before passing to a detailed consideration of the stomach, it is important to know that the microscopic examination of the kidneys revealed a far advanced glomerulonephritis of sufficient degree to account for uremic manifestations and even death



Fig 1—Mycotic gastritis The flat membranous deposit encircling the cardio-esophageal junction (*a*) extends distally over the surface of the stomach (*b*) A longitudinal section has been removed from the elevated, ragged excrescence (*c*)

Gross Description of the Stomach—A well demarcated, greenish-gray membranous deposit (fig 1 *a*) of rather irregular outline, averaging about 1 cm in width, encircled the cardio-esophageal junction The prolongation (*b*) of this membrane passed distally over the region of the lesser curvature of the stomach for a distance of 3.5 cm Most of the membrane was firmly attached to the underlying structure, especially on the gastric side, but in some areas it could be readily separated The deposit was of uniform thickness and followed the folds of the

mucous membrane in its undulations. Contiguous with the membranous ring, there was found at the lesser curvature just beyond the cardia an elevated, olive-shaped, ragged mass (*c*) which measured 4 cm in length and 1.5 cm in its widest diameter, it was situated 13 cm above the level of the gastric mucous membrane at its highest point. The center of the growth overlay the left gastric artery at the point of origin of several of its main branches. The long axis of this mass followed the line of the lesser curvature. The tissue which comprised this peculiar, shaggy prominence was a dirty greenish-gray and was soft, friable and irregular. The anterior and inferior margins of the growth were sloping, whereas the posterior and superior margins were slightly overhanging or straight. The surface of the growth, in general, was curved. In one place at the antero-inferior portion, an area approximately 0.5 cm in diameter was discolored red

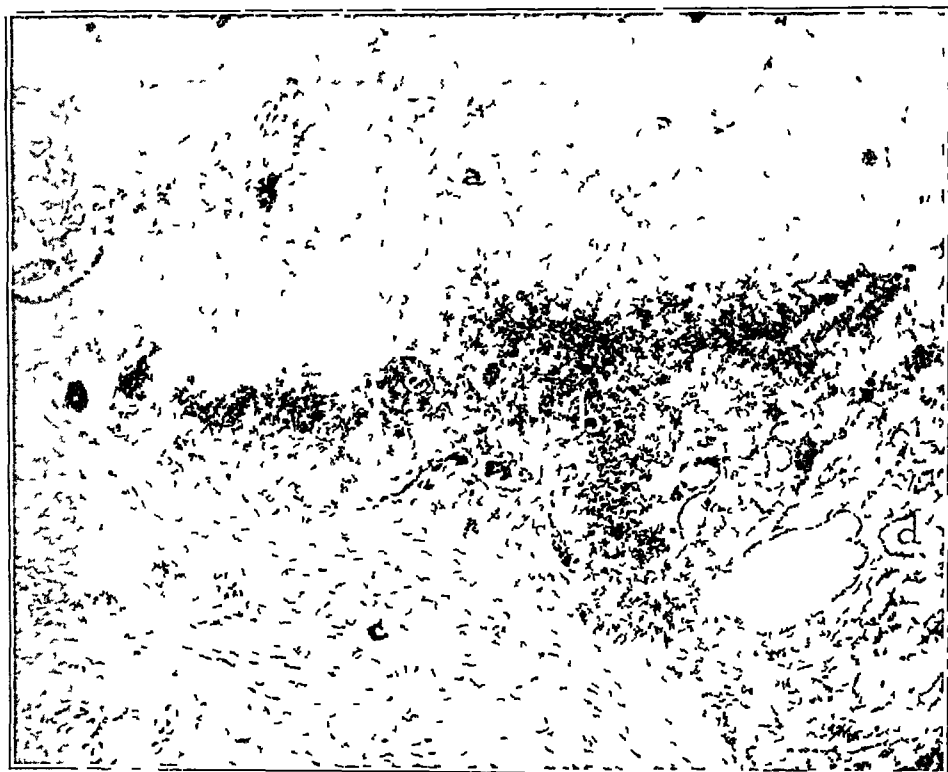


Fig 2—A section taken from the margin of lesion (*c*), figure 1. The necrotic layer (*a*) is delimited by a highly cellular zone (*b*) beyond which (*c*, *d*) the inflammatory reaction diminishes in intensity. One thrombosed vessel (*e*) can be readily identified.

by blood. When the growth was sectioned in its longitudinal axis, the greenish-gray mass was observed to have coalesced intimately with the mucous membrane, which had lost its architecture and could not be identified. The structureless tissue extended to the muscularis, which appeared to be intact. In a transverse section of the prominence, the well demarcated borders were more clearly seen, they were studded in many places with hemorrhagic extravasations and thrombosed blood vessels, which extended into the greenish-gray substance. At the anterior and inferior margins, where the mass sloped, the structureless, hemorrhagic tissue was seen to have insinuated itself between the mucosa and the subjacent layer, which raised the former but did not depress the latter. Evidence of previous ulceration,

either acute or chronic, could not be found at the site of the lesions mentioned. The stomach appeared to be unchanged except for the localized involvement described.

Microscopic Examination—Using a lens of low magnification (fig 2), one could distinguish three separate zones in sections taken from the involved areas of the stomach. The upper (superficial) one (a) consisted of a necrotic mass, which in the case of the largest lesion was heaped up far above the level of the bordering mucous membrane, and extended downward into the wall of the stomach to involve, in places, the entire thickness of the mucosa and part of the submucosa. In sections taken from the regions of the flat deposits, the necrosis was seen to be more superficial, rarely reaching to the muscularis mucosae. The second zone (b), which more or less sharply separated the previous one from the

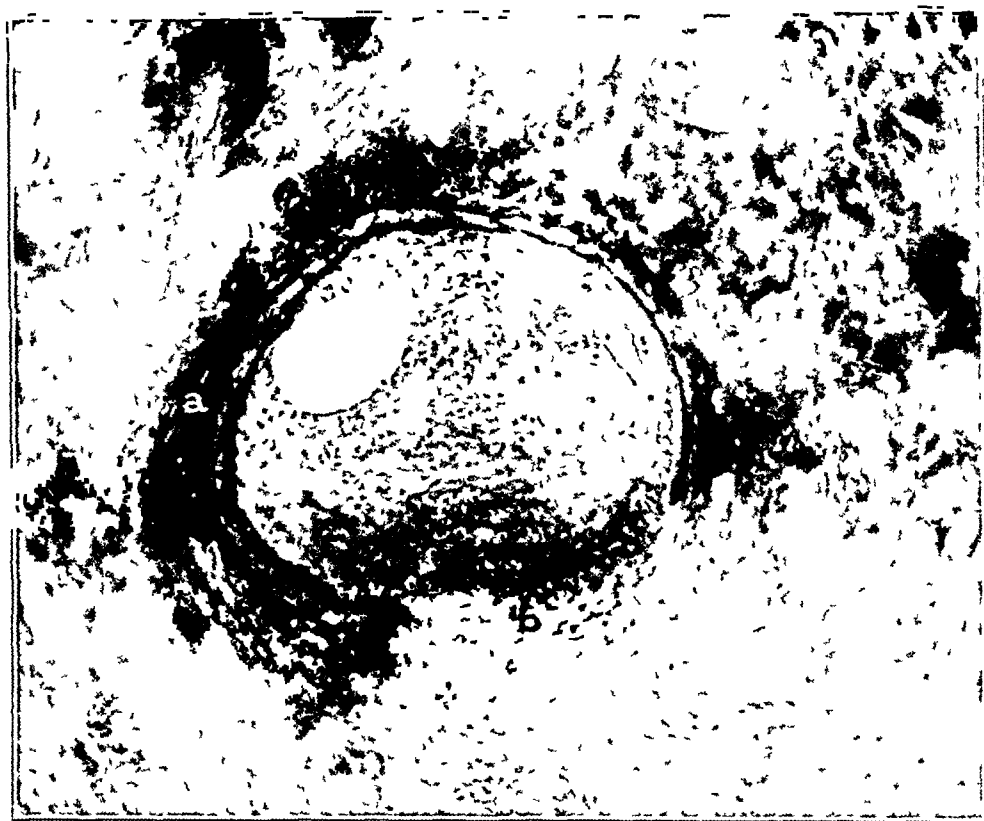


Fig 3—Photomicrograph of a thrombosed blood vessel located in the necrotic layer (fig 2 a). In approximately three fourths of the circumference of the wall calcific deposits (a) are found, the remaining one-fourth (b) appearing relatively normal.

third, was represented by a dense band rich in cellular elements, with some hemorrhagic extravasations. The third zone (c) was occupied by relatively normal appearing tissue.

The necrotic zone, when viewed with a lens of higher magnification, was seen to be made up of structureless, pink material with many blue-staining foci, situated especially in the superficial layers and consisting of granular masses the morphology of which could not be identified in hematoxylin and eosin stained sections. The only elements in this area which retained their structure sufficiently to permit recognition were the blood vessels (fig 2 c), the walls of some of which were fairly well preserved while others were represented by mere

shadows Most remarkable, however, was the presence of calcific deposits in the walls of a number of blood vessels In one such vessel (fig 3), the deposition of lime (*a*) embraced approximately three fourths of the circumference of the vascular wall, while the remaining one-fourth (*b*) presented a relatively normal appearance Recent hemorrhage is indicated by the presence of intact red blood cells found more particularly near the surface of the lesion

The necrotic and the relatively normal zones were separated by an area of intense inflammatory reaction which for the most part demarcated the living from the dead tissue more or less sharply This limiting membrane was composed of many round cells, together with a moderate number of polymorphonuclear leukocytes, macrophages and plasma cells These cells were densely packed in some places, and separated by edema fluid and fibrin in other places Proliferative changes were not prominent, there were a few spindle-shaped fibroblasts, and only slight multiplication of the endothelial cells had occurred At the margins of the inflammatory zone, the glandular elements of the mucosa showed little evidence of growth Within this demarcating wall, the vessels were dilated and distended with blood Rupture of some of the blood channels had apparently occurred and was indicated by the presence of free red cells and blood pigment

When one passed to the third zone, a more or less gradual transition to the normal was seen, and the reactive phenomena became less and less marked toward the serosa, so that this layer and the muscularis appeared to be practically unchanged This description applies particularly to the main lesion (fig 1 *c*) Sections taken from areas covered by the flat membranous deposit (fig 1 *a* and *b*) showed essentially the same processes in varying degrees of extent and intensity Histologic examination of the wall of the stomach at points remote from the grossly visible lesions disclosed a diffuse infiltration of the interglandular stroma of the mucosa by round and plasma cells in rather large numbers Although thick walled vessels were frequently encountered in the mucosa of the grossly normal portions, calcification of the vascular walls was nowhere observed

In sections stained by the Gram-Weigert method, the surface of the necrotic area appeared to be purplish-violet In many places, the violet material extended irregularly into the deeper parts, gradually becoming less dense and finally fading out into the fine processes The purplish-violet material, which for the most part was limited to the upper half of the necrotic layer, did not extend beyond the zone of inflammatory reaction Under oil immersion magnification, it was found that the deep-staining masses on the surface were composed of spherical bodies of different sizes, all, however, were considerably larger than cocci These globoid structures exhibited a distinct tendency to form irregular groups, the smallest of which were composed of from four to sixteen round elements In the larger groups, the spheres were often so densely packed as to obscure their individual characteristics Many fine, long threads were found lying between the round bodies in the deeper part of the purplish-blue material These filaments (fig 4), especially with a change of focus, showed distinct branching (*a*), which for the most part was angular The free end of many of the threads showed bulbous thickenings Many of the filamentous elements were made up of round granules arranged in linear formation (*b*) In the deeper parts of the necrotic layer, the spheroidal bodies were lacking, and only the filaments could be seen These were found to invade a number of the small blood vessels, apparently having penetrated the adventitial and muscular coats Well preserved threads were not noted in the lumen of the thrombosed vessels

COMMENT

In the light of the postmortem observations, it appears reasonable to assume that the epistaxis and bleeding from the mouth were to be ascribed indirectly to the marked changes in the kidneys. To what extent nephritis was responsible for the gastric symptoms and what effect the mycotic gastritis had on the function of the stomach were somewhat conjectural. The old blood clot obtained by lavage performed the second day after admission to the hospital might well be attributed to the swallowed blood following the nasal packing. The emesis of blood clots and a small amount of bright red fluid recorded on the third day after entrance could likewise be explained (although with less prob-

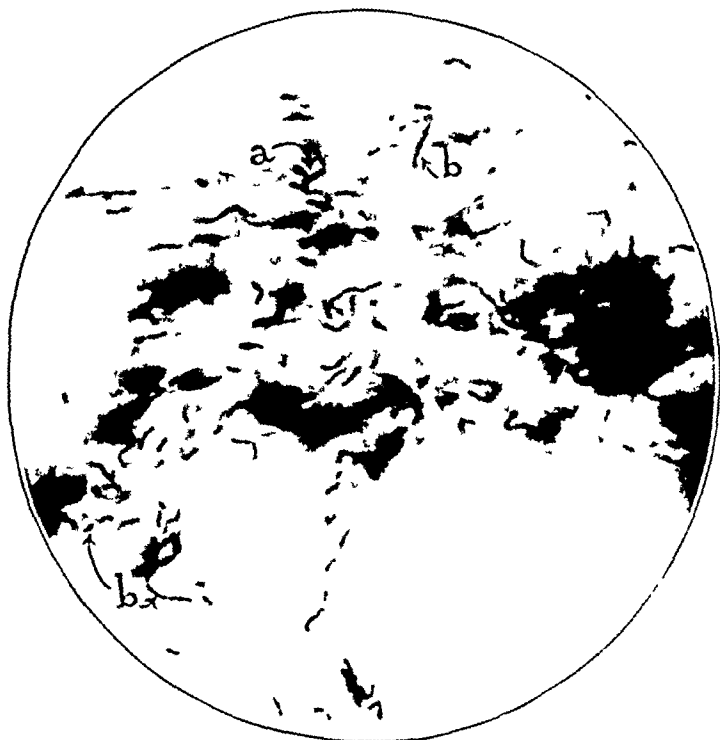


Fig 4—Threadlike organisms in the deeper portions of the necrotic area. One of the filaments shows distinct branching (*a*) while several are granular (*b*)

ability) on the same basis. It is likely, however, that the hematemesis which occurred hourly on April 10 was due to the effect of the fungous growth. It was this history of vomiting of blood, together with the appearance of the lesion, which led Dr. Jaffe to diagnose mycotic gastritis at the autopsy table. The fungus from the morphologic appearance seemingly belonged to the streptothrix (*Nocardia*) group, the spheroidal bodies representing spores (*Conidia*) and the branched threads, mycelia.

GROSS PATHOLOGIC LESIONS OF MYCOTIC GASTRITIS

In a survey of the literature on mycotic gastritis, one is struck by the diverse and widely different lesions in the individual cases. In an attempt

at classification, the possibility suggested itself that these various lesions might represent different stages in the same process. If one reviews the separate reports with this thought in mind, it will be found that practically all of the pictures described can be satisfactorily explained on one pathogenic basis. The essential lesion is a focal inflammatory one, associated with vascular damage, which is apparently responsible for the accompanying necrosis. The development of the mycotic lesion finds a somewhat rough analogy in the genesis of the ulcer resulting from typhoid. The first stage in mycotic gastritis is characterized by formation of membrane due to the parasitic growth, followed by hemorrhagic necrosis of the underlying mucous membrane, production of slough and ulceration.

The membrane may develop in an intact stomach, in that event, however, general debility or a catarrhal inflammation of the gastric mucosa (Maresch²¹) is usually present, or the mycotic infection may be secondary to a gastric imperfection which favors the lodgment of molds on the defective site. In a case described by Klebs,²² microscopic examination showed that the patient had an intact epithelium covered by a membrane consisting entirely of fungi. Such a case may be considered one of primary mycotic gastritis. Marchand²³ related that an 18 year old girl partook of a dish of decomposed mushrooms which, according to this author's interpretation, led to multiple hemorrhagic erosions, some of which were invaded secondarily by molds. It is difficult and at times impossible to distinguish between primary mycotic lesions associated with hemorrhage and hemorrhagic erosions on which a fungous growth has developed secondarily. The cases of gastric ulcer in which the presence of molds can be demonstrated, but in which little if any change is discernible in the gross appearance of the primary lesions, are not to be looked on as instances of mycotic gastritis.

The membrane which forms as a result of the fungous growth varies in color, frequently being green or gray and at times yellow or white. An admixture of brown or red, presumably due to imbibition of blood pigment, is commonly seen. The appearance of the membrane is similar to that observed in the pharynx and esophagus and, in fact, closely resembles a growth cultivated on an artificial medium. The deposits, which may be hemispherical, are, as a rule, elevated and flat, and often centrally depressed. These membranous deposits usually are

21 Maresch, R. Zur Kenntniss der Soormykose des Magens, *Ztschr. f. Heilk.* **28** 145, 1907.

22 Klebs, E. *Handbuch der pathologischen Anatomie*, Berlin, 1869, vol. 2, pt. 1, p. 20.

23 Marchand. Ein eigentümlicher Magenbefund (Ulcus gangraenosum durch Fadenpilzwucherung) nach Vergiftung durch verdorbene Steinpilze, *Verhandl. d. deutsch. path. Gesellsch.* **14** 183, 1910.

sharply demarcated from the adjacent mucosa and not infrequently are surrounded individually by a narrow pale ring followed by a hyperemic hemorrhagic circular zone. The concentric arrangement of the rings gives the whole lesion the appearance of an iris.

The size of the individual lesion varies from that of a pinhead to a diffuse growth covering a broad surface or even the entire stomach. In von Wahl's²⁴ case, in which mycotic gastritis was first reported, the lesions were yellowish prominences the size of a pinhead and larger, they were isolated and coalescent and resembled the pustules of smallpox. In his case, Zalesky²⁵ described disseminated and confluent gray-white hemispherical and flat projections, varying in size from that of a pinhead to that of a lentil, and possessing central umbilication which likewise suggested a resemblance to the pustular eruption of variola. In Meyenburg's¹¹ third case, a group of tiny pustule-like prominences were found in the stomach of the patient. The lesions are as a rule larger than those described, in most of the cases varying in size from that of a lentil to several centimeters in diameter. Two involved areas are reported in Marchand's²¹ case, one 2 by 3.5 cm, the other 4.5 by 6.5 cm, to be present in the patient. Buhl²⁶ related that in his case of gastric and intestinal mycosis there were sixty-two foci, varying in size from 2 mm to 7 cm in diameter. Occasionally a terrace-like arrangement formed by several colonies is encountered. In Lohlein's²⁷ first case, three such layers could be raised from each other. In Beneke's²⁸ report, the essential lesion consisted of a yellowish-green area made up of concentric deposits surrounding an ulcerated center. The lesions are practically always circular, except when they become confluent, in which event irregularity of outline results. A single extensive deposit is rarely found. In the case of the 18 months' old infant reported by Plaskuda,²⁹ the membrane involved not only the pharynx and esophagus, but extended beyond the cardia over almost the entire surface of the stomach to form a complete gray-brown lining of the gastric lumen. From the standpoint of height, a great variety in the lesions is noted. In Meyenburg's¹¹ three cases, the surface of the membrane extended just barely above that of the surrounding mucosa, measuring from 0.1 cm to 0.15 cm in height. As a

24 Von Wahl, E. Ueber einen Fall von Mykose des Magens, Virchows Arch f path Anat **21** 579, 1861

25 Zalesky, N. Ein Fall von Soor im Magen Virchows Arch f path Anat **31** 426, 1864

26 Buhl, L. Mycosis intestinalis, Ztschr f Biol **6** 129, 1870

27 Lohlein, M. Ueber Schimmelmikosen des Magens, Virchows Arch f path Anat **227** 86, 1919-1920

28 Beneke, R. Ein Fall von Schimmelpilzgeschwür in der Magenschleimhaut, Ztschr f Path **7** 1, 1911

29 Plaskuda. Hauterkrankungen bei kachektischen Kindern. 1. Fall von Purpura mit ausgebreiteter Soorbildung im Magen, Berl Klin **1** 501, 1864

rule, the level of the growth appears to be from 0.2 to 0.5 cm. In my own case, the development is a most luxuriant one, as the level of the lesion extended 1.3 cm above that of the mucosa. There is an extreme variation in the number of foci, as recorded in some of the foregoing statements.

Necrosis of the superficial layers of the gastric wall underlying the central portion of the lesion occurs relatively early, and is demonstrated best in a cross-section (gross as well as microscopic) of the involved focus. This change is indicated by a crater formation, which lends more height to the margins of the lesion. In Buhl's²⁶ patient, a prominence 2 cm in diameter with central umbilication appeared as though it were the seat of a superficial ulcer, a second larger lesion presented a similar appearance. The author called attention to the possible deception, for in both instances there was central depression without the loss of tissue substance. Teutschlaender³⁰ spoke of a tendency toward rather than real ulceration in these cases, with central necrosis and crater formation. As a matter of fact, it is difficult, at times, to decide from the gross appearance alone whether the excavation is the result of central necrosis and depression or of actual separation and extrusion of dead tissue.

The necrotic zone being, as a rule, well demarcated, sloughing readily occurs. The ulcer which follows is usually a superficial one. In von Meyenburg's³¹ first case, five umbilicated defects in the mucosa were found, two of which were originally covered by black sloughs that were loosened in manipulation even though the specimen was carefully handled. In addition to a single large lesion, 5 cm in diameter, with a slightly sunken center, on the wall of the stomach, Maresch²¹ described a circumscribed defect which, according to this author, apparently represented the site of a previously cast-off slough. There were also three foci of necrosis covered by delicate deposits only slightly adherent to the underlying tissue. Lohlein's²⁷ second case was that of a patient who presented nine flat, sharply bordered ulcers which for the most part had fairly smooth, pale yellow floors. Some of these ulcers were circular or somewhat oval, others were irregular, apparently dependent on the outline of the cast-off slough, which was not always round. In many cases, the floor of the ulcer was uneven and shaggy and discolored dark red or black by blood, as in the cases of von Recklinghausen,³¹ Beneke²⁸ and others. Although the ulceration is usually superficial, the necrosis at times extends deep into the gastric wall. In Benelli's³²

30 Teutschlaender, O. Mucormykose des Magens, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **29** 127, 1917.

31 Von Recklinghausen, F. Multiple Nekrosen der Magenschleimhaut, (*a*) Mykose der Magenschleimhaut, *Virchows Arch. f. path. Anat.* **30** 366, 1864.

32 Benelli. Mykose der Magenschleimhaut, *Beitr. z. Path. Anat. u. z. allg. Pathol.* **54** 619, 1912.

case, the patent did not have a funnel-shaped perforation, but a diffuse peritonitis was found which this author attributed to invasion of the entire thickness of the stomach wall by fungus

The gastritis is not focal in all cases. Von Meyenburg³³ related a case in which the patient had puerperal sepsis complicated by a phlegmon of the stomach. Microscopic examination of the gastric wall showed a widespread invasion of the involved parts with mycelia. The author assumed the rather diffuse phlegmonous gastritis to be on a mycotic basis and secondary to the uterine infection. Askanazy¹⁰ described a case of acute diffuse oidiomycotic gastritis which occurred in a 68 year old person following the operative removal of a pyloric ulcer and a gastro-enterostomy undertaken four days before death. The gross specimen presented the appearance of a diffuse, hemorrhagic, gelatinous inflammation. In many instances the mycotic lesions are not limited to the stomach. In a case of mycotic gastritis reported by Maresch,²¹ the process extended to the stomach from a carcinoma of the esophagus. In one of von Meyenburg's³³ cases, the patient had metastatic abscesses on a mycotic basis in the liver. In a number of reports, esophageal involvement in the absence of ulceration in this organ is noted, particularly in children (Nauwerck,³⁴ Plaskuda,²⁹ Zalesky²⁵). In a unique case, that of Buhl,²⁶ in addition to the involvement of the stomach, duodenum and intestines a marked mesenteric and retroperitoneal lymphadenitis, a hemorrhagic periadenitis and a bloody peritoneal exudate were found.

MICROSCOPIC APPEARANCE IN THIS CONDITION

From what has been said regarding the variations in the gross appearance of mycotic lesions, the degree of microscopic dissimilarity in the various cases can be deduced. Here, however, owing to the relative ease in identification of the pathologic processes, the changes in the separate reports lend themselves readily to classification. Teutschlaender¹⁰ summarized the microscopic changes found in his patient under the following heads: necrosis, cellular infiltration, tissue proliferation, hyperemia, hemorrhage, edema, exudation of fibrin and vascular thrombosis. These processes in differing degrees and combinations represent the alterations described by other authors. The various changes can be grouped under the title of hemorrhagic inflammation with thrombotic tendencies.

33 von Meyenburg, H. Ueber einen Fall von Fadenpilzgeschwüren der Magenschleimhaut mit metastatischen Abzessen in der Leber, *Virchows Arch. f. path. Anat.* **229** 30, 1920.

34 Nauwerck, C. Mykotisch-peptisches Magengeschwür, *München med. Wehnschr.* **42** 877 u. 908, 1895.

The membrane, as a rule, consists of intertwining mycelial elements which are frequently branching, often associated with ovoid or globose bodies (conidia), together with desquamated epithelial cells, leukocytes and cellular debris. At times, the morphology of the fungus is sufficiently characteristic in the histologic preparations to permit identification, as in Lohlein's²⁷ case, in which aerial hyphae carrying the distinctive fructification bodies led to recognition of the mold as *Aspergillus fumigatus*. According to Castellani and Chalmers,³⁵ the fungi often lose their characteristics when growing parasitically in the tissues, and only mycelial threads and round and oval yeastlike bodies are seen. This statement is borne out by von Meyenburg's¹¹ observation of a case in which *Aspergillus fumigatus* was obtained in culture, but the microscopic sections showed only branching threads and globoid swellings devoid of fructification forms.

The epithelial surface underlying the membrane may be intact, but most often superficial necrosis is met with, even in the early cases. The zone of necrosis usually corresponds to the central portion of the overlying membranous deposit, and assumes the form of a blunt wedge with the apex directed outward toward the serosa. The extent of the necrosis varies, but it usually does not spread beyond the muscularis mucosae. The membrane due to the death of the parasites also participates in this necrosis. Within this zone of dead tissue, evidence of hemorrhage, in the form of blood pigment both free and engulfed, is a prominent feature frequently associated with the outlines or shadows of thrombosed vessels.

Bordering the necrotic zone is a leukocytic wall in which polymorphonuclear forms most frequently predominate. Some of these cells are laden with blood pigment and fatty detritus. Associated with this cellular infiltration are the usual changes of inflammation. Particularly marked at times are the proliferative changes involving not only the spindle shaped and endothelial cells of the submucosa, but also the epithelial elements of the mucosa. The distribution of the exudative and proliferative changes correspond roughly to the location of the invading molds. The depth to which the mycelia penetrate differs in each case, extension to the serosa, as in Ljubimowa's³⁶ report, being exceptional.

Most remarkable in the microscopic picture, however, is the tendency of the organisms to invade the blood vessels, presumably leading to extensive thrombosis and hemorrhage, which characterize mycoses of the stomach as of other organs. The vascular changes, in turn, account

35 Castellani, A., and Chalmers, A. J. Manual of Tropical Medicine, New York, 1920, ed. 3.

36 Ljubimowa, W. J. Ein Fall von Ulcus ventriculi verursacht durch Schimmelpilze, Virchows Arch. f. path. Anat. **214** 432, 1913.

for the necrosis *en masse* of the superficial layers, which, likewise, is a distinctive feature of the typical lesion. Lohlein²⁷ postulated a chemotactic attraction for fungi by the circulating blood to account for the invasion of the muscle layer of the arterial wall by these organisms. The theory of the entrance of molds into the blood stream from a primary site in the throat was invoked to explain the multiple abscesses of the brain containing grossly visible mycotic colonies in the case described by Zenker³⁷. In the later years, Wagner,³⁸ and subsequently Vogel,³⁹ were able to substantiate Zenker's assumption by demonstrating the organisms in histologic preparations of the walls of blood vessels. It was not, however, until Heller⁹ discovered the presence of fungi in one third of the twenty-five cases he studied that the frequency of invasion of vessels was emphasized. The foregoing reports are concerned exclusively with pharyngeal and esophageal involvement.

The first observation of vascular invasion of the stomach by molds is credited to Pariot,¹⁰ who described this phenomenon in children. In practically all reports of mycotic gastritis, including and following Marchand's²³ report, the presence of fungi in the walls of the stomach was noted. Whereas thrombosis is the usual outcome in the esophageal vessels, the added danger of peptic erosion is incurred in the stomach. Fungi are held responsible for profuse hemorrhage in a case reported by Pick.⁴¹ The patient was a woman, aged 44, who, following a septic abortion, developed hematemesis and melena. The lesion, according to Pick, consisted of a small chronic ulcer in the floor of which a suppurative process had developed, which in turn led to erosion of a subjacent vessel. The suppuration was produced purely as a result of mycotic organisms, the elements of which could be seen in histologic sections invading the arterial wall. Askanazy¹⁰ cited three similar cases (cases 18, 19 and 20) of hemorrhage complicating an ulcer associated with the presence of fungi. In the stomach of a patient who died from gastric hemorrhage, Meike¹ found a penetrating ulcer with an eroded vessel. The author attributed the fatal hemorrhage to the destructive effect of the branched mycelia which were found in the arterial wall. In all the cases of severe fatal hemorrhage mentioned, the primary lesion appears to have been a chronic round ulcer in which the base became secondarily involved by mycotic infection.

37 Von Zenker, F. A. Krankheiten des Oesophagus, in von Ziemssen Handbuch der speziellen Pathologie und Therapie, 1874, vol 7, p 192

38 Wagner, E. Zur Kenntnis des Soors des Oesophagus, Jahrb f Kinderh 1868

39 Vogel, A., in von Ziemssen Handbuch der speziellen Pathologie und Therapie, 1874, vol 7, p 64

40 Parrot, referred to by Heller. Beitrag zur Lehre vom Soor, Deutsches Arch f klin Med 55:116, 1895

41 Pick, L. Arterienarrosion durch Soorpilze mit tödlicher Blutung, ein Beitrag zur Kenntnis der Oidiomykosen, Berl klin Wchnschr 57 798, 1920

BACTERIOLOGY OF MYCOTIC GASTRITIS

Owing to the fact that cases of mycotic gastritis are so seldom recognized before the histologic examination reveals the true nature of the disease, bacteriologic studies are, as a rule, omitted. In a few instances, however, cultures have been made from the fresh material, or smears or teased preparations have been examined. In the case of a man, aged 58, who died from carcinoma of the esophagus and mycotic gastritis, Maresch²¹ was able to cultivate *Aspergillus fumigatus*. He injected a growth of this organism into rabbits and produced a generalized mycosis. In von Meyenburg's¹¹ first case, the same organism was isolated in pure culture (except for the presence of *Bacillus subtilis*). In the cases reported by Rudnew,⁴² the lesions were invaded by an organism identified as *Penicillium glaucum*. In Kundrat's⁴³ case of universal favus, lesions harboring the characteristic molds were found in the esophagus, stomach and large bowel. In the cases of Marchand,²³ Beneke,²⁸ Ljubimowa³⁶ and Teutschlaender,³⁰ the fungi were identified by morphologic criteria as belonging to the mucor group. In histologic preparations of his first case, Lohlein²⁷ was able to demonstrate aerial hyphae bearing fructification forms indicating an infection with *Aspergillus fumigatus*. It is not to be inferred that in all cases of aspergillosis characteristic forms of the organism appear in the tissue, for in von Meyenburg's¹¹ case, as previously mentioned, although the organism was identified culturally, the characteristic forms were not present in the histologic sections which would permit recognition. Von Meyenburg stated that the higher fungi are found especially in acute lesions, and that the lower molds are more frequently encountered in chronic cases. In the case herein reported, the circumstances and conditions under which the autopsy was performed did not permit immediate culture. It appears from a morphologic study that the causal organism belongs to the streptothrix (*Nocardia*) group.

SYMPTOMATOLOGY

It is difficult to formulate a definite clinical picture of a mycosis of the stomach, since the disease is usually encountered as the terminal event of an independent condition. Which manifestations to attribute to the primary illness and which to the complicating disease, is in a great measure conjectural. Even in cases of primary mycotic gastritis the evaluation of symptoms is not an easy task, owing to the frequent occur-

42 Rudnew referred to by Petterson, A. Zur Frage der Bedeutung der Fadenpilze für die pathologischen Veränderung des Magens, Deutsche med Wchnschr 28 703 1902

43 Kundrat, H. in Schmidts Jahrbucher Ueber Gastro-Enteritis favosa 206 253 1885

rence of secondary bacteriologic invasion. Clinical recognition of fungus infection of the stomach, as for instance by gastroscopic examination or at operation, which up to the present has not been recorded, would aid materially in identifying the symptoms due solely to the effect of the molds.

From a study of the reports in the literature, it may be stated that in the average case in which the mycotic process is limited to the stomach the infection does not produce constitutional disturbance. When, however, as it occasionally happens, the fungus involvement is extensive, the general manifestations may be profound. The symptoms are those of an acute infection, without distinctive characteristics. In Buhl's²⁰ case, the numerous lesions throughout the gastro-intestinal tract of the patient were held accountable, in the absence of other pathologic processes, for the vomiting, collapse and death of the patient. At times, the gastric mycosis leads indirectly to systemic effects by permitting secondary invaders to gain entrance into the previously healthy tissues. In one of von Mevenburg's¹¹ cases the general toxemia suggested the clinical diagnosis of typhoid fever. At autopsy, a mycotic gastritis and multiple metastatic abscesses of the liver were found. As von Meyenburg was able to demonstrate bacteria and no fungi in the hepatic abscesses, he considered the gastric mycosis the portal of entry for the pyogenic organisms that reached the liver. A somewhat similar case, a mycotic gastritis complicated by a diffuse purulent peritonitis, was reported by Benelli.¹² Clinically, the patient presented gastro-intestinal symptoms, followed by evidence of peritonitis. At autopsy fungi were found in the gastric lesion, but not in the peritoneal exudate. The author considered the fungus infection of the stomach as the primary lesion through which the entrance of bacteria into the peritoneal cavity occurred. In those cases in which an independent infectious process is present, as for instance in pneumonia, which existed in my own patient, a consideration of all the facts is necessary before assignment of systemic symptoms to any single cause is made.

In regard to the local manifestations difficulty is likewise encountered in attempting to segregate the symptoms produced by the mycotic from those resulting from a concomitant condition. Zalesky²¹ reported the case of a bottle-fed infant who died with gastro-intestinal symptoms on the eighteenth day of its life. The writer ascribed the vomiting and diarrhea to the extensive mycotic involvement found at the autopsy, although if one reads the clinical history, the possibility of a primary nutritional disturbance to account for the symptoms readily suggests itself. In my own case of mycotic gastritis, the explanation of the hematemesis, in view of the associated high grade nephritis and the history of bleeding from the nose and mouth, is by no means unequivocal.

As Teutschlaender³⁰ pointed out, the vomiting, especially the vomiting of blood, is the only symptom that can be assigned to fungus infection of the stomach. The finding of molds in the aspirated gastric contents is in itself of little diagnostic importance, but when associated with repeated vomiting of small amounts of blood, it might lead to the suspicion that a mycotic gastritis was present. When the hematemesis is severe, the underlying lesion is more likely to be a peptic ulcer, in the floor and walls of which fungi may or may not be present.

SUMMARY

From what has been stated regarding the relative rarity of mycotic gastritis, its occurrence most frequently (in the light of present knowledge) as a terminal event or complication and the inability to detect its presence by ordinary diagnostic methods, it is to be concluded that the condition is of little clinical importance. One gains the impression, however, that a final decision regarding the rôle of fungi, in primary and secondary disease of the stomach, should be withheld until further data have been accumulated. It is striking that in so many cases the nature of the lesion is recognized only after careful study. In a case in which death followed resection of a duodenal ulcer, Lang⁴⁴ identified a *leptothrix*, apparently from the ulcer, as the cause of the pyelephlebitis and cholangitis that contributed to the patient's death. Just how frequently the presence of fungi is overlooked in similar cases is difficult to estimate. The indications are that molds are responsible for many infections in which bacteria are incriminated. More frequent routine search for fungi as well as for bacteria would aid in determining the frequency and importance of mycotic organisms in gastric disease.

44 Lang, F. J. Durch *Leptothrix*-Infektion bedingte Leberinfarction in einem Falle von callosem Ulcus duodeni, *Virchows Arch f path Anat* **234** 367, 1921.

THE POSSIBLE INCREASE OF GUANIDINE IN THE BLOOD OF CERTAIN PERSONS WITH HYPERTENSION ¹

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In a recent communication ¹ we described a method for the determination of guanidine bases in the blood, and noted that certain patients suffering from arterial hypertension showed higher values than did normal persons.

Since this publication, the work has been carried forward and a definite improvement in the method has been achieved. The method differs from that previously described in that the guanidine bases are absorbed by blood charcoal from a filtrate made slightly alkaline, and subsequently are released from the charcoal by means of acidified alcohol. The details of this method have been described elsewhere,² but a summary of it will be given before discussing the results obtained.

METHOD

(1) Nitroprusside reagent

Stock solution

- 10 per cent sodium nitroprusside
- 10 per cent potassium ferricyanide
- 10 per cent sodium hydroxide

Mix

- 1 volume 10 per cent sodium nitroprusside
- 1 volume 10 per cent potassium ferricyanide
- 1 volume 10 per cent sodium hydroxide

Add 3 volumes of water to 1 volume of the mixed reagent.

The reagent is ready for use when the color has changed to a pale yellow, which takes about twenty minutes. One cubic centimeter of the reagent is employed for every 5 cc of the solution to be tested. This reagent will ordinarily keep for twelve hours, but if a turbidity develops after a few hours a fresh solution should be made for use.

(2) Blood charcoal—Merck's—purified by acid

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1 Major, Ralph H, and Weber, C J. The Probable Presence of Increased Amounts of Guanidine in the Blood of Patients with Arterial Hypertension, Bull Johns Hopkins Hosp **40** 85, 1927.

2 Weber, C J. The Determination of Guanidine Bases in the Blood, Proc Soc Exper Biol & Med **24** 712, 1927.

(3) Acidified alcohol—95 per cent alcohol containing 2 cc of normal hydrochloric acid per hundred cubic centimeters

(4) Standard guanidine solution

Stock

Dissolve 0.1542 Gm of guanidine carbonate solution in 100 cc of 0.1 normal hydrochloric acid and add a few drops of chloroform as a preservative. This solution contains 1 mg of guanidine per cubic centimeter.

Standard

Ten cubic centimeters of the stock solution made up to 1,000 cc with distilled water gives a solution containing 0.01 mg of guanidine per cubic centimeter.

Procedure

Twenty cubic centimeters of blood are precipitated with tungstic acid as in the regular Folin-Wu procedure. (The two-thirds normal sulphuric acid is added first and then followed by the tungstate which enables one to obtain 50 cc of filtrate more quickly.) Eighty cubic centimeters of the filtrate is taken and 6 drops (0.4 to 0.5 cc) of 10 per cent sodium hydroxide added, followed by 0.5 Gm of blood charcoal. (This may be added by means of a spoon, which delivers the proper amount—a 4 inch horn spoon is suitable.) The charcoal is brought into suspension by shaking and after two to five minutes, the mixture is filtered through a 9 cm folded filter, care being taken to avoid loss of charcoal. The flask is drained as completely as possible, but the charcoal is not washed. After the filter paper has drained for five minutes, the charcoal and filter paper is put back into the same flask from which filtration was made. Twenty-five cubic centimeters of the acidified alcohol is now added and the flask corked tightly and shaken vigorously to bring the charcoal into suspension. The shaking should be repeated several times during the two hour period so that the charcoal is left in contact with the alcohol. The charcoal may be left in contact with the alcohol over night, when the yield will be slightly greater.

The charcoal is filtered from the alcohol, and 20 cc of the alcoholic filtrate is evaporated to dryness on a water bath. (Care must be taken not to produce charring. The safest plan is to keep the temperature of the water bath just below boiling and to assist the evaporation with an electric fan.)

The residue is taken up in 7 cc of water. One cubic centimeter is set aside for the creatine determination and 1 cc for the creatinine determination. One cubic centimeter of the nitroprusside reagent is then added to the remaining 5 cc. The solution is poured into a centrifuge tube and centrifuged for about two minutes, to throw down the slight flocculant precipitate which forms at this point. The supernatant liquid is decanted into a colorimeter cup and read against the appropriate standard which was prepared simultaneously with the unknown.

Standard tubes

Four tubes containing 2 cc, 3 cc, 4 cc and 6 cc of the standard guanidine solution are each made up to 10 cc, and 2 cc of the reagent is added. If necessary, an extra tube containing 10 cc of the standard guanidine solution may be added.

Calculation

Standard set at 20

$$\frac{20}{\text{Reading of unknown}} \text{ by } \frac{\text{mg in standard}}{2} \text{ by } 21.9 = \left\{ \begin{array}{l} \text{mg of guanidine bases calcu} \\ \text{lated as guanidine per hundred} \\ \text{cubic centimeters of blood} \end{array} \right.$$

Since creatine produces some color with this reagent, it is necessary to make a correction for it. When making the creatine estimations on final filtrate, a

correction of 0.12 must be applied. Thus, if the reading is 1 mg of guanidine and the creatine content of the final filtrate is 2 mg per hundred cubic centimeters, the figure $2 \times 0.12 = 0.24$ must be subtracted from 1 mg. The correct reading then would be 0.76 mg of guanidine.

This procedure differs slightly from the method described by Weber, since the creatine estimations for the correction are made on the final filtrate, instead of on the Folin-Wu filtrate.

Although creatinine may produce color with this reagent, the development of color is much slower than in the case of guanidine. If the reading is made within five minutes of mixing the solution, the color produced by 1 mg of guanidine is as great as that produced by 400 mg of creatinine. The amount of creatinine in normal blood does not interfere with the readings. Creatine, on the contrary, develops the color rapidly, and a correction must always be made for its presence, as stated. The color obtained after correction for creatine is not due to creatine, since it persists after conversion of creatine into creatinine by autoclaving in an acid solution. We have not, however, removed the creatine before making determination, since experiments have shown us that autoclaving also diminishes, to some extent, the color given to the blood filtrate to which a known quantity of guanidine has been added. Urea is not present in the final filtrate and does not cause interference.

We have tested the accuracy of this method by the addition of known amounts of guanidine to the blood and have found that the average recovery has been 85 per cent when amounts varying from 0.2 mg to 1.0 mg per hundred cubic centimeters were added. The recovery is as high as 75 to 85 per cent, when amounts as small as 0.2 to 0.3 mg per hundred cubic centimeters were employed—a percentage of recovery higher than by the older method. Because of possible variations in the chemicals employed and particularly in the blood charcoal, a series of recoveries have been carried out with each new batch of chemicals before employing the method.

The results obtained in a series of thirty-five persons with normal blood pressures are given in table 1. The average guanidine reading obtained in these patients has been 0.11 mg per hundred cubic centimeters. Variations have been from 0.02 to 0.19 mg. Nearly one half of these readings showed less than 0.1 mg per hundred cubic centimeters. These values are somewhat lower than those given by the previous method, although it was stated at that time that the accurate estimation of amounts lower than 0.2 mg per hundred cubic centimeters could not be made by the older method. The modification of the method gives clearer filtrates which are more easily read, and permits the estimation of smaller amounts.

A series of readings in patients with arterial hypertension, most of them being cases of "essential hypertension" is shown in table 2. The series also includes some cases of nephritis with nitrogen retention. The table shows that although some of the patients with "essential hypertension" show normal values, the majority of the patients with "essential hypertension" show some increase over the normal "guanidine" values.

TABLE 1—*Guanidine Readings Obtained in a Series of Thirty-Five Persons with Normal Blood Pressure**

No	Age	Blood Pressure	Protein Nitrogen	Creatinine	Uric Acid	Guanidine Reading	Corrected	Remarks
1	40	120/70	35.3	1.3	3.0	2.8	24	06
2	36	110/80	31.5	1.25	3.9	2.8	25	02
3	35	110/80	26.1	1.15	3.6	2.36	26	04
4	47	132/80	33.3	1.4	4.6	5.0	5	22
5	29	128/82	30.8	1.25	3.2	3.4	26	06
6	21	120/86	30.8	1.4	3.0	4.1	25	07
7	39	120/86	32.4	1.3	3.0	3.7	24	06
8	40	134/96	33.3	1.4	3.1	3.46	24	05
9	59	120/70	28.6	1.36	2.8	3.64	36	19
10	43	110/80	32.0	1.4	3.8	2.53	36	13
11	26	120/80	34.7	1.4	4.7	2.66	4	12
12	37	108/86	32.0	1.3	4.6	2.66	32	04
13	60	104/76	34.8	1.25	3.6	2.85	38	16
14	36	100/70	40.0	1.3	3.2	1.75	38	19
15	54	154/84	30.8	1.3	3.7	2.16	38	16
16	47	100/58	35.6	1.25	3.75	3.2	39	17
17	18	100/54	36.3	1.2	3.8	2.4	36	14
18	48	120/80	32.0	1.25	3.2	2.16	38	18
19	46	122/84	26.6	1.3	3.8	3.12	32	12
20	48	154/90	30.7	1.25	3.7	2.76	35	13
21	40	150/90	27.6	1.25	4.2	2.85	33	08
22	50	94/54	34.8	1.25	3.6	2.76	36	14
23	50	122/86	40.0	1.4	3.6	2.96	38	16
24	42	122/84	43.0	1.3	4.6	3.6	43	15
25	50	146/74	30.5	1.25	3.7	2.6	31	09
26	23	90/60	24.5	1.1	4.1	3.3	33	08
27	28	110/104	27.6	1.2	4.0	3.6	31	07
28	27	103/62	21.5	1.3	4.3	2.0	36	11
29	47	140/80	29.2	1.3	4.9	3.46	38	09
30	30	125/95	41.5	1.5	4.0	4.3	43	19
31	68	150/80	35.0	1.4	4.1	4.1	38	13
32	26	122/80	25.7	2.0	3.7	3.1	32	10
33	40	135/90	34.5	1.2	3.8	2.4	24	02
34	70	150/86	30.3	1.2	2.5	3.6	24	03
35	40	160/100	36.0	1.3	4.6	2.7	47	11

* Blood chemistry in milligrams per hundred cubic centimeters of blood

dine" values, while the patients with nephritis and nitrogen retention show marked increases in "blood guanidine."

These observations suggest the importance of two pertinent inquiries: Are the slight increases in the group of "essential hypertension" of any significance? Can the increase in "blood guanidine" in chronic nephritis be due to an error of the method in oxidizing the increased amounts of creatinine present in the blood of these nephritic patients into methyl guanidine?



Fig 1 —Dog injected with two doses each 10 mg methyl guanidine sulphate per kilogram of body weight Blood pressure taken at beginning of experiment was from 120 to 130 mm The last injection was made five minutes before the portion of the curve shown Note the continuous elevation of the blood pressure with blood guanidine varying from 0.29 to 0.38 mg per hundred cubic centimeters

We have studied the first question by observing the increases in the blood guanidine produced by the injection of sufficient amounts of methyl guanidine sulphate to elevate the blood pressure. These observations were made on six dogs and three of the curves are shown in figures 1, 2 and 3.

TABLE 2—*Guanidine Readings in a Series of Patients with Arterial Hypertension**

No	Age	Blood Pressure	Protein Nitrogen	Creatinine	Creatine	Uric Acid	Guanidine Reading	Corrected	Remarks
1	54	180/120	40.0	1.6	5.6	5.0	57	41	
2	50	156/110	35.7	1.3	4.9	3.1	44	27	
3	36	200/134	33.3	1.4	5.2	4.0	44	28	
4	74	176/110	30.0	1.3	4.6	3.3	22	13	Marked arteriosclerosis
5	70	192/130	37.0	1.3	3.1	4.1	33	16	Marked arteriosclerosis
6	40	176/110	37.5	2.0	4.5	5.4	36	09	Diabetes
7	48	190/112	35.0	1.5	4.8	4.1	42	13	Carcinoma of breast
8	72	175/110	29.0	1.4	3.8	2.4	23	04	Arteriosclerosis
9	51	194/130	86.0	3.6	5.1	5.3	65	39	
10	40	180/130	315	12.0	5.6	5.3	11	67	Chronic nephritis
		170/120	183	18.5		8.0	24	23	Chronic nephritis uremia
11	27	200/140	97.8	8.3		4.7	49	28	Chronic nephritis
		200/140	89.0	11	1.4	3.9	67	54	Chronic nephritis
		180/130	77.0	8.7	6.7	5.0	94	45	Chronic nephritis
12	45	210/100	33.0	1.2	3.0	2.7	38	2	
13	47	180/120	30.0	1.1	2.9		38	21	
14	63	196/98	31.0	1.3	2.7	3.2	33	12	Aortic insufficiency
15	34	180/110	28.7	1.3	5.0	3.3	4	1	
16	44	185/120	28.0	1.2	3.8	3.6	48	25	
17	48	144/80	48.0	1.7	4.5	5.1	6	33	Hemiplegia cardiac failure
18	57	190/130	39.6	1.4	4.5	3.46	34	07	
19	30	160/120	37.0	3	3.3	2.75	38	18	
20	57	178/124	37.5	2.4	3	3.2	43	25	
21	65	180/120	33.0	1.3	4.2	6.1	32	26	
22	55	178/95	35.0	1.3	3.7	4.7	32	25	
23	66	214/130	36.5	1.1	3.2		44	28	
24	24	160/110	188.0	13.7	2.3		1.6	1.3	Chronic nephritis uremia
25	66	214/130	36.5	1.1	3.2		44	28	
		220/134	33.0	1.3			42	3	
26	35	240/140	91.0	4.9	5.1	6.1	46	15	
			156.0	9.6	10	9.4	1.2	68	
27	42	190/120	92.0	4.3	3.5		46	25	
		170/110	31.0	1.2	6.2		56	3	
28	47	180/120	40.0	1.9			62	48	
29	68	234/130	33.0	1.2	5.6	4.1	55	29	
30	32	255/145	30.0	1.5	4.3	3.6	31	14	
31	54	180/120	34.0	1.2	4.6	6	31	19	
32	43	180/120	30.0	1.6	5.3	3.8	27	16	
33	42	170/110	31.0	1.5	5.1	4.9	36	17	
34	39	240/130	35.3	1.8	4	4.9	33	22	
35	65	200/130	71.0	2.6	3.5		33	2	

* Blood chemistry in milligrams per hundred cubic centimeters of blood

The curves show that a blood guanidine increase from 0.14 to 0.28 mg per hundred cubic centimeters may be sufficient to produce a marked elevation in blood pressure. Such values are no higher than those obtained in many patients with arterial hypertension and suggest strongly that the increases noted in certain hypertensives, if they are really due to guanidine, are sufficient to produce an elevation in blood pressure.

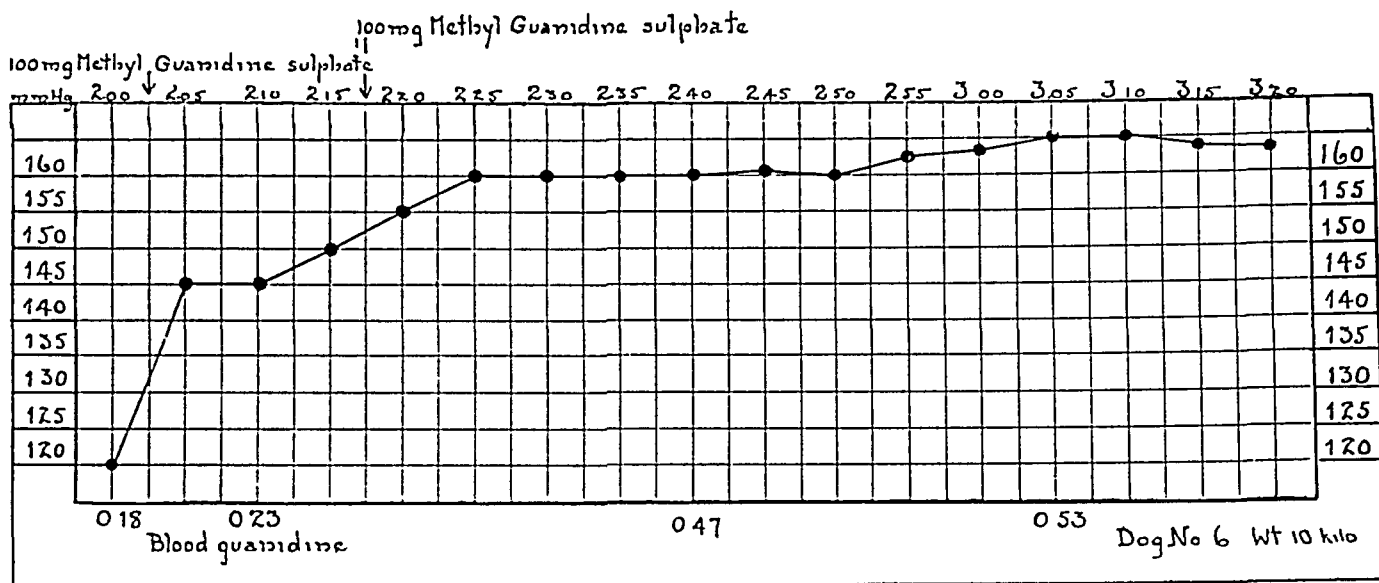


Fig 2—Curve drawn from complete tracing of an experiment There was a marked elevation of blood pressure with only moderate increase in blood guanidine

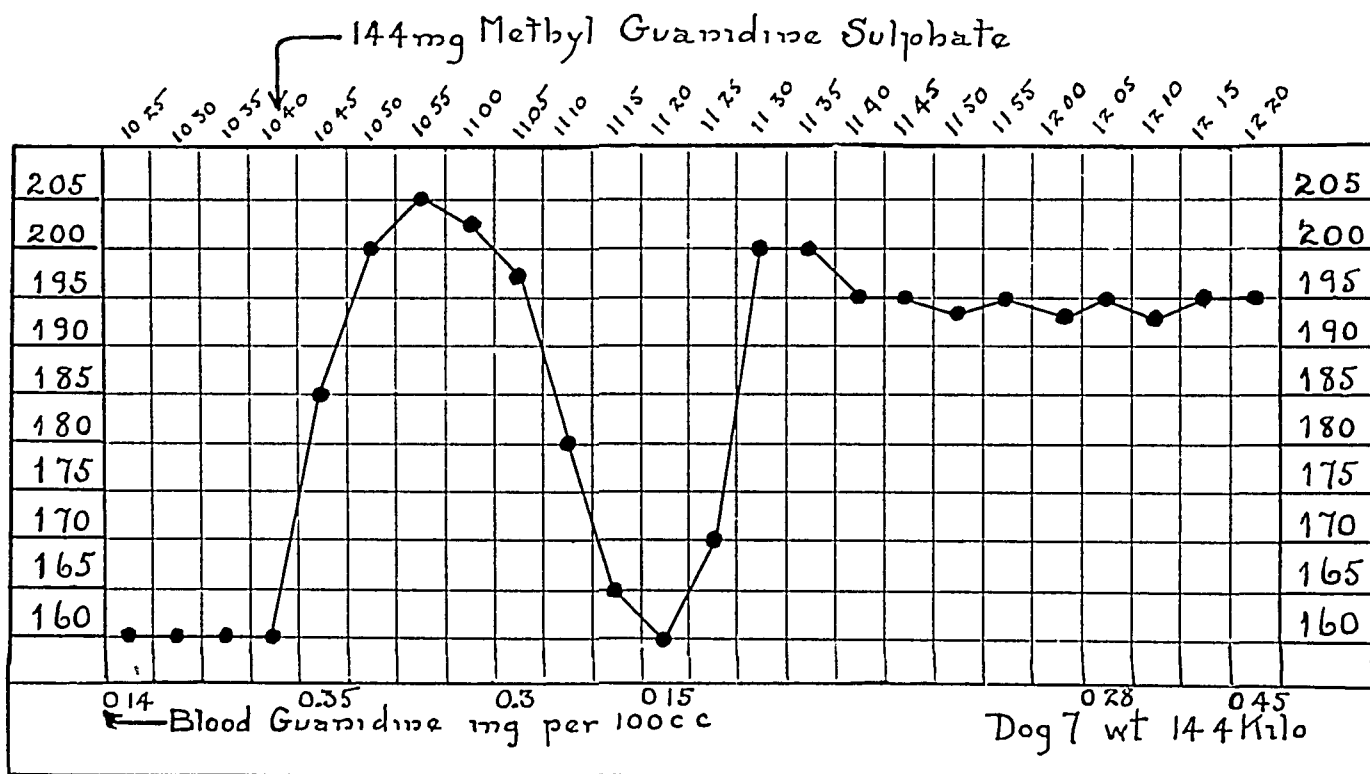


Fig 3—Observation similar to figure 2 Note the sudden fall in blood pressure, accompanied by a lowering in blood guanidine, then a subsequent rise Such fluctuations are not uncommon The explanation of them is not apparent

The possible conversion of creatinine into methyl guanidine by the method with a resulting error in the patients having high blood creatinine, was studied in a series of experiments. In these experiments, definite amounts of creatinine (Eastman) were added to samples of blood which were then examined for guanidine by the method described in this article. The results are shown in table 3.

These observations show that the added creatinine does not produce change in the color reaction as compared with the control until the blood creatinine reaches the high value of 20 mg per hundred cubic centimeters or more. The increase in the final blood "guanidine" value with 20 mg of creatinine per hundred cubic centimeters is only 0.1 mg, so

TABLE 3—*Results of a Series of Experiments in Which Creatinine is Converted Into Methyl Guanidine*

Blood No. 1	Creatinine Added per Hundred Cubic Centimeters	Reading	Blood Guanidine (uncorrected)
Normal		(1)	0.42
Normal		(2)	0.44
Normal	5 mg	(1)	0.42
Normal	5 mg	(2)	0.42
Normal	10 mg	(1)	0.44
Normal	15 mg	(1)	0.44
Normal	25 mg	(1)	0.5
Normal	35 mg	(1)	0.54
Blood No. 2			
Normal		(1)	0.38
Normal		(2)	0.33
Normal	10 mg	(1)	0.36
Normal	10 mg	(2)	0.37
Normal	10 mg	(3)	0.38
Normal	10 mg	(4)	0.38
Normal	20 mg	(1)	0.51
		(2)	0.47
		(3)	0.50

it seems impossible that the high guanidine values in patients 10, 11 and 24 were due to the increase in blood creatinine in these patients.

We have studied four patients with uremia, all of whom have shown high "guanidine" blood values. In one patient with uremia, not included in this series because of a difference in the method of determination, the high blood "guanidine" of 3 mg per hundred cubic centimeters was seen.

In dogs, we have frequently seen convulsions after the injection of methyl guanidine sulphate when the blood showed 1 mg guanidine per hundred cubic centimeters, or higher. This suggests that if the increase in the color reaction in the blood of these patients with uremia is actually due to guanidine, it may be present in amounts sufficient to produce toxic effects such as convulsions.

We realize that we do not have any proof that the color reaction in the blood is due to guanidine. The reaction is, however, given by

guanidine, which is a pressor substance. We have found increased amounts in fifty observations on patients suffering from arterial hypertension, including six cases of frank nephritis. The final proof that this color reaction is due to guanidine can only come with the isolation of guanidine from the blood, and if it is present only in the small amounts indicated by the colorimetric examination, such isolation will probably be extremely difficult.

EXPERIMENTAL OBSTRUCTIVE JAUNDICE

I GROWTH FACTOR IN DEFECTIVE CALCIFICATION *

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It is our purpose to present in this paper the roentgenographic evidence of a high grade osteoporotic condition developing in the long bones of jaundiced puppies and to give further data on the blood calcium of these animals. The results obtained from a study of several litters enable us to present a more comprehensive report and to substantiate the observation made recently¹ that a fairly uniformly progressive calcium deficiency occurs during this early period of growth. Whereas progressive loss in weight and cachexia obtain for the jaundiced adult animal, the young one shows a progressive gain in weight which is appreciable at the time of death, although emaciation may have supervened. Investigators in this field have limited themselves entirely to a study of the adult animal, and extended work has not been carried out on the very young. It seemed advisable, therefore, to investigate further the disturbances which might be expected to arise in the growing young animal with its low storage of calcium.

METHODS

These experiments extended over a period of twelve months. Five litters, comprising twenty-four puppies from 8 to 10 weeks old, were used. The puppies in two litters were allowed to live their span of life after the induction of jaundice, and those in three litters were used for another set of experiments before the twentieth day of jaundice (thyroparathyroidectomized). Four control animals were kept. One of the animals on which operation was performed served as an excellent control in that it reestablished a bile flow to the intestine through regeneration of the bile passages. The common duct was divided between ligatures in nine animals, eleven in addition to this had their gallbladders removed.

* Read before the American Physiological Society, Rochester N Y, April 14, 1927

* From the Nelson Morris Fund and the John D and Fannie K Hertz Fund of the Michael Reese Hospital, the Nelson Morris Institute for Medical Research, and the Department of Physiology of the University of Chicago

1 Buchbinder, W C, and Kern, Ruth. Blood Calcium Deficiency in Experimental Obstructive Jaundice, *Am J Physiol* **80** 273 (April) 1927

The animals were allowed to run free in a room. They were taken outdoors almost daily for a short while, even during the winter months. Their diet consisted of various kinds of meat, raw and cooked, dog biscuits, cooked vegetables (including tomatoes) and cooked cereals. Orange juice was added to the diet. The animals were allowed a liberal quantity of milk (3 quarts to five animals). During transient periods of anorexia, milk constituted their chief diet. The animals were allowed to eat as much as they desired.

A record of the animals' weights was kept. Determinations of blood calcium were made at the beginning of the experiment and during the period of jaundice at intervals of from ten to twenty days. The Kramer-Tisdall² technic was used, and duplicate determinations were made, except in few instances. Roentgenograms of the front extremities of all animals were made at the beginning of the experiment. They were taken in three litters of the puppies from sixteen to eighteen days after the induction of jaundice, in two litters, between the sixtieth and seventieth day of jaundice.

Electrocardiograms were made of the animals of the latter group, and an accurate record was kept of the pulse rates. The results obtained from this part of the experiment will be published as a separate report.

RESULTS

An examination of the data given in tables 1 and 2 (charts 1 and 2) for nineteen jaundiced puppies after twenty days of induced jaundice did not reveal significant changes in the blood calcium level, although there was a suggestion of lowering. At this time the gain in body weight (nine animals) amounted to 16 per cent. The animals showed definite signs of impaired nutrition and were slightly less active than the normal controls. They acquired a distaste for certain foods, and at times their appetites were capricious. Generally it was equal to that of their nonjaundiced mates, and it was often voracious. Vomiting was rarely noted. The stools were clay colored, and often liquid and spotted with blood.

An increase in body weight was noted up to the sixtieth day, at that time amounting to 66 per cent (five animals). The percentage of decrease in the blood serum calcium was almost equal to that of the gain in body weight (56.6 per cent decrease in blood calcium for four animals). Not only was there a complete absence of neuromuscular irritability, but there was some degree of apathy. At this time, a greatly

² Kramer, B., and Tisdall, F. F. A Clinical Method for the Quantitative Determinations of Calcium and Magnesium in Small Amounts of Serum and Plasma, *Bull. Johns Hopkins Hosp.* **32**: 44 (Feb.) 1921.

increased growth of skeletal structures was noted (fig 1) Between the seventy-fifth and one-hundredth day the animals did not fare so well and lost weight Although marked emaciation may have supervened before death, their body weight was considerably above that at the time jaundice

TABLE 1—*Calcium Determination for Calcium in Blood Serum of Jaundiced Puppies*

	Initial Calcium	Days After Induction of Jaundice											
		10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100	100-110	120-130	
Queenie	13.2		12.1			9.5				9.6			
Gretchen	11.8		11.9			9.3, 8.7							
Whitefoot *	11.6		12.0		11.1			10.9		11.9			
Sandy *	12.9		12.3		10.9			11.5		11.8			
Sarah *	10.2		8.0		7.0	†	6.7		10.8	10.3			
Bimbo	10.5	10.4		8.0									
Mike	10.2	9.9	8.8			7.0	5.1			5.0	7.0	6.2	
Doc	13.2		11.8	Died during the second operation									
Mary	12.1	10.8			8.2		7.8			8.2			
Bubbles	9.9		6.7		5.8		7.1, 5.4						
Average	11.6	10.4	10.4	8.0	7.0	8.5	6.4			8.3	7.0	6.2	

* Control animals

† Jaundice clears up, urine free of bile pigment Autopsy revealed reestablishment of bile flow to the intestine

TABLE 2—*Determinations for Calcium in Blood Serum of Puppies Jaundiced from Sixteen to Eighteen Days (Animals Were Then Thyroparathyroidectomized)*

	Initial Calcium	
Ann *	11.7	14.4
Cinder *	10.5	14.1
Tan	10.1	11.6
Wolf	10.2	11.1
Cinderella	9.9	9.5
Bob	8.5	8.5
Brownie	13.4	9.6
Spotty	11.8	10.3
Ulysses	12.0	9.7
Hermine	12.7	9.7
Tippy	12.4	10.1
Ear	11.6	11.3
Sacro	11.2	8.7
Averages	11.2 (13)	10.0 (11)

* Control animals

was initiated They finally showed signs of severe chronic intoxication Alternating periods of ascites and hydiemia with dehydration states were noted in two animals This probably most readily accounts for the rise in the blood calcium in the last stages of jaundice (table 1, dogs 1 and 10) They also developed a relative tachycardia with

inversion of the T-wave of the electrocardiogram. In this respect, the effects of prolonged obstructive jaundice appear to be cumulative.

Roentgenographic studies made on three litters in which the animals were jaundiced for twenty days did not reveal any changes in bone density or structure, they were altogether like those of the controls. Roentgenograms taken from sixty to seventy days after the induction

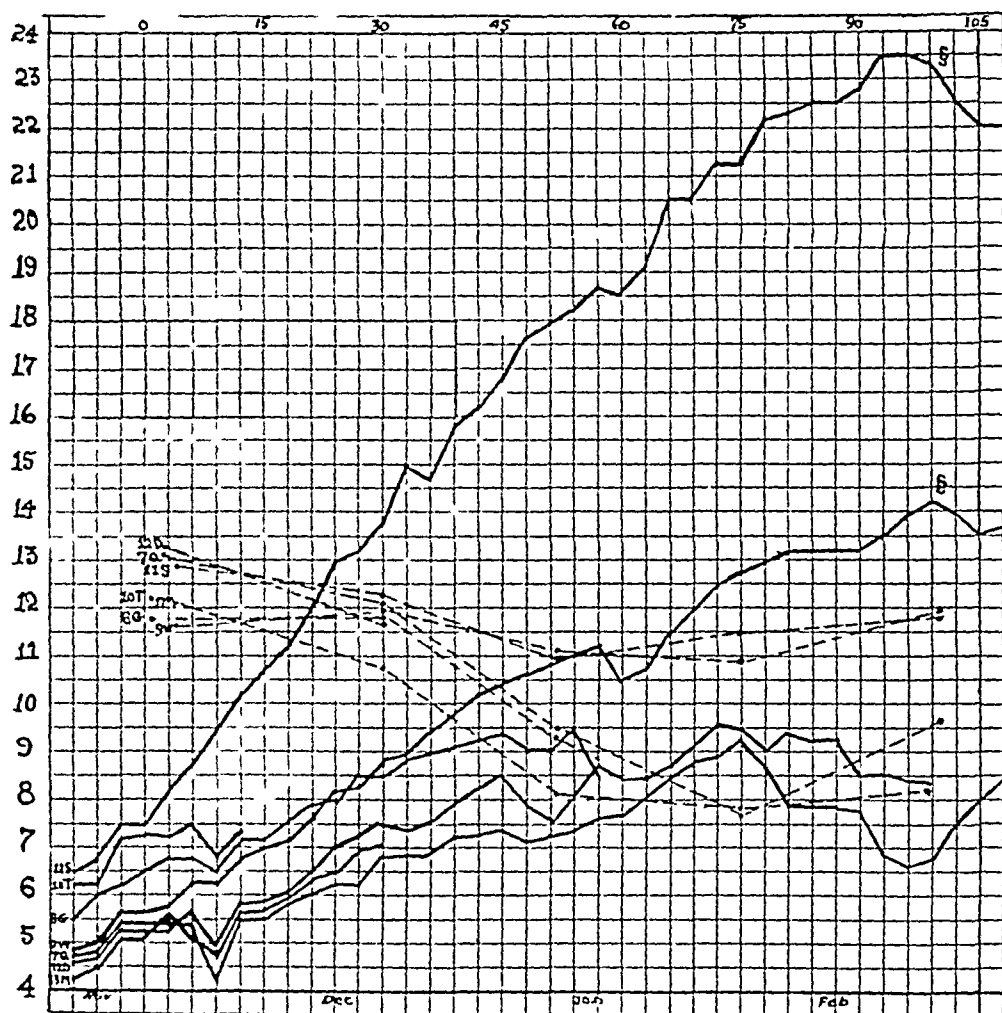


Chart 1—Decrease in blood serum calcium with an increase in body weight in a litter of animals. The broken line indicates the calcium, and the unbroken line the weight. Numbers 11 S and 9 W show the curves for the control dogs. The § indicates the division of the common duct in control dogs. The ordinates represent milligrams of calcium per one hundred cubic centimeters of blood and pounds of body weight. Each division of the abscissa represents three days.

of jaundice disclosed a high grade rarefaction, cortical thinning with relatively wide medullary spaces and a lack of contrast generally. This is best shown by a comparison of the metatarsal bones of the jaundiced animals with those of the controls (figs 2, 3, 4 and 5).

REVIEW OF LITERATURE

Since the first quantitative studies of the calcium balance in obstructive jaundice by King, Bigelow and Pearce were published,³ a number of reports have appeared on the blood calcium in jaundice. Although numerous methods have been employed, results obtained point almost uniformly to constant and normal calcium values. Snell, Greene and Rowntree⁴ found a practically constant and normal calcium value, and Snell,⁵ using the Kramer-Tisdall technic, found that the blood calcium remains well within the normal range in many jaundiced patients and

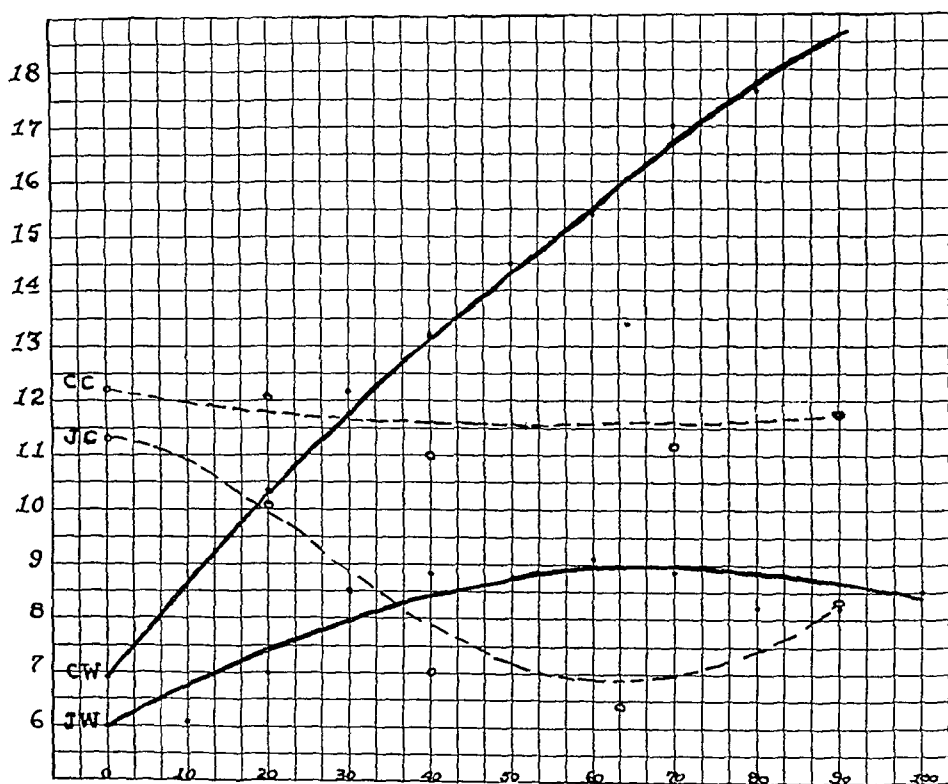


Chart 2—Composite graph of the calcium and body weight curves. The ordinates represent pounds in body weight and milligrams of calcium per one hundred cubic centimeters of blood. The hollow circle and broken line indicate the calcium. The curve marked C C shows the calcium for the control dogs and that marked J C, the calcium for the jaundiced dogs. The solid circle and unbroken line indicate the body weight (for only two animals). The abscissas represent days after the induction of jaundice.

3 King, J. H., Bigelow, J. E., and Pearce, L. Experimental Obstructive Jaundice, *J. Exper. Med.* **14** 159 (Aug) 1911.

4 Snell, A. M., Greene, C. H., and Rowntree, L. G. Diseases of the Liver II. A Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice, *Arch. Int. Med.* **36** 273 (Aug) 1925.

5 Snell, A. M. Personal communication.



Fig 1—Growth of skeletal structures is evident in the dogs at either end of the group that were jaundiced seventy-five days Both dogs have marked ascites The animal in the center is a control The three are litter mates Roentgenogram of the dog in the left is seen in figure 4



Fig 2—Normal physiologic depositions of lime salts the result of growth

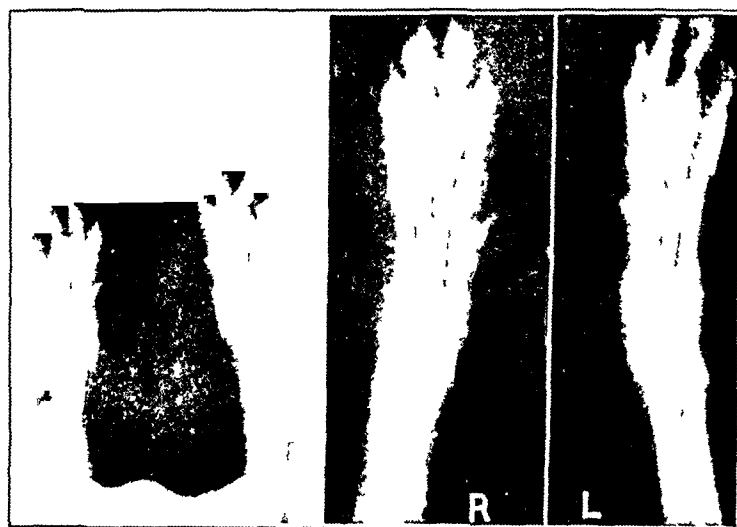


Fig 3—Normal physiologic depositions of lime salts the result of growth

animals The observations of Koechig,⁶ Halvorson, Mohler and Bergheim,⁷ who used other methods for determinations for calcium, are in agreement with the foregoing

The quantitative studies of King, Bigelow and Pearce disclosed a loss of calcium from certain of the tissues, notably bone and heart, and an increase in the calcium of the blood The bone of the jaundiced dog

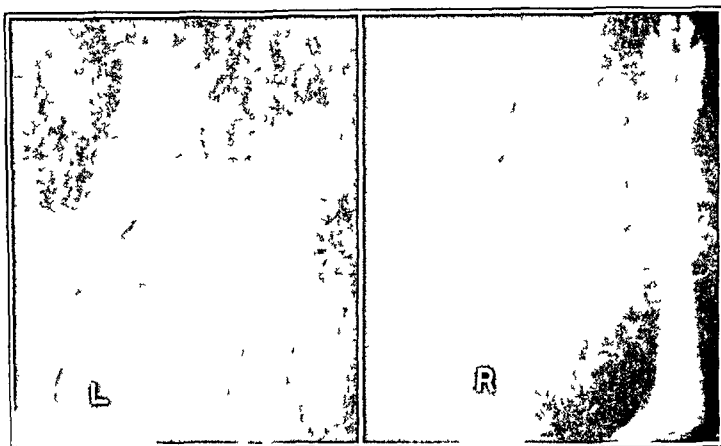


Fig 4—Roentgenograms of the prejaundiced state and that sixty days after the induction of jaundice A comparison of the metatarsals of these animals and those shown in figures 2 and 3 reveals a distinct thinning of the cortex, relatively wide medullary spaces and a lack of film contrast



Fig 5—The same conditions are illustrated here as in figure 4

showed a striking loss, which pointed to this organ as furnishing most of the calcium to combat an intoxication Hypercalcemia in jaundice has not been noted by subsequent investigators, nor have we been able to

6 Koechig, I The Calcium Control of the Blood in Pathologic Conditions, *J Lab & Clin Med* **9** 679 (July) 1923

7 Halvorson, J O , Mohler, H K , and Bergheim, O The Calcium Content of the Blood Serum in Certain Pathological Conditions, *J Biol Chem* **32** 171 (Nov) 1917

find any reference to other quantitative studies applied to skeletal structures in this state. Their finding of a loss of calcium in the heart throws some doubt on the accuracy of their entire work since, in his researches Collip⁸ disclosed a special affinity of this organ for calcium in hypercalcemic states following the use of his extract.

The pioneer work of Rohrig⁹ in investigating the cardiovascular effects of bile resulted in the conclusion that bile owes its toxicity to the bile salts. Most investigators have been of this opinion.¹⁰ King and Stewart¹¹ presented evidence that the toxicity of bile is due to the pigment, and afforded some evidence as to how calcium may serve the organism in a physiologic and protective fashion. They showed that the lethal dose of uncombined pigment corresponded almost exactly to the amount of pigment in the lethal dose of whole bile, and that when a prepared calcium biliverdinate was injected into the circulation, toxic effects were absent. More recently, Walters and Bowler,¹² studying the rate of excretion of calcium chloride in the jaundiced and normal animal, showed a marked avidity of the former for calcium. It required about two times the amount of injected calcium to raise the blood calcium level of the jaundiced animal to the same level as that of the normal one in spite of the fact that the blood calcium content was practically the same in the jaundiced and normal animals before and after the injection of a lethal dose. This suggested to these authors a calcium deficiency that was not apparent.

COMMENT

The nutritional state of our animals varied at the beginning of the experiment, and it was common to note rachitic changes. Some of the animals developed cretinoid characters (fig. 6), but an increase in the length of long bones was always observed. The roentgenograms revealed this in all instances. Growth potentialities of animals of mixed breeding even though of the same litter are factors that have to be reckoned with, especially in designating controls. There is, however, a constant striking contrast in the calcification processes of what we

8 Collip, J. B. Harvey Lectures, Baltimore, Williams & Wilkins Company 1925-1926, p. 142.

9 Rohrig, A. *Arch. d. Heilkunde*, **4** 385, 1863.

10 Since the manuscript was completed, Horrall has reported his conclusion that the only toxic agents in bile are the salts of the bile acids. (Horrall, O. H. Toxicity of Bile, *Am. J. Physiol.* **81** 486 [July] 1927.)

11 King, J. H., and Stewart, H. Effect of the Injection of Bile on the Circulation, *J. Exper. Med.* **11** 673 (Sept.) 1909.

12 Walters, W., and Bowler, J. P. The Preoperative Preparation of Patients with Obstructive Jaundice. An Experimental Study of the Toxicity of Intravenous Calcium Chloride Used in the Preparation of Patients, *Surg. Gynec. Obst.* **39** 200 (July) 1924.

have assumed to be normal physiologic growth and those occurring in the jaundiced animals of the same litter. Quantitative methods need to be applied to determine whether the changes in bone are the result of lysis, i. e., the removal of calcium from bone already formed, or of actual but deficient deposition of lime salts into an increased matrix.

We have enumerated the chief intrinsic factors operating in the production of the faulty calcification as follows (they are concurrent, and it is difficult without quantitative data to evaluate them). First, the total body calcium in the animals used in the experiment is small. Sherman and MacLeod¹³ have shown that in mice there is an increase in the percentage of body calcium from 0.25 to 0.6 per cent after the first fifteen days of existence. A correspondingly longer interval for



Fig. 6—Animal jaundiced 100 days. Note the cretoid characters. This animal developed bilateral bone cysts (fig. 5).

such an increase could be expected in the dog. Second, a grave metabolic disorder is present, osteoblastic tissues should have an extremely unfavorable environment in which to build bone. Third, there is an intestinal factor, the effect of the exclusion of bile from the intestine apart from the serious digestive disturbances that arise. Finally, there is a growth factor, new bone production exceeds the rapidity with which lime salts are deposited.

The normal blood calciums that obtain in the adult animal throughout the course of obstructive jaundice when the same serious digestive disturbances arise would speak against any great defect in the capacity of the intestine to absorb calcium. In the young animal that has been jaundiced twenty days, significant changes in the blood calcium level

¹³ Sherman, H. C., and MacLeod, F. L. The Calcium Content of the Body in Relation to Age, Growth and Food, *J. Biol. Chem.* **64**: 429 (June) 1925.

are not noted. If changes in the skeletal structures of the adult animal occur in late obstructive jaundice, such observations have escaped clinical recognition. On the other hand, the severe osteoporosis that develops in the animal with a persisting fistula of the biliary tract is well established. Pawlow¹⁴ and his co-workers noted this, and more recently Whipple¹⁵ called attention to the thinning of the bone, the loss of inorganic salts and a tendency to spontaneous fracture in this condition. Osteoporosis has also been observed in man¹⁶ with fistulas of the gallbladder. Total exclusion of bile from the intestine is the only thing obviously in common in the two gross disturbances of the biliary tract, in obstructive jaundice, a retention of the biliary constituents in the blood and tissues follows. Such evidence would tend to support the idea that a close relationship exists between the extrahepatic functions of bile and the metabolism of bone. In the young animal, in which anabolic processes predominate, perhaps the loss of vitamins, antirachitic factors, and possibly the absence of some catalytic agent normally present in bile, may also play important rôles in the production of faulty calcification.

A slight lowering of the calcium in the blood serum is to be noted thirty days after the induction of jaundice. At this time the roentgenogram does not reveal significant changes in the density of bone structure although quantitative studies might disclose such changes. The high degree of rarefaction parallels the marked lowering of the blood calcium after from forty to fifty days of induced jaundice. It might therefore be argued that here, as in other states of calcium diam, the structural changes are secondary. The belief that some rôle of the parathyroids in maintaining free from tetany those animals with low calcium values, the animals exhibiting not the slightest neuromuscular irritability but actually some degree of apathy, would further support the notion that such a mobilization had occurred. Calcium values in the blood might still remain low as a result of either increased excretion or some precipitating mechanism already mentioned. The progressiveness of the calcium deficiency also calls for an explanation, even though we are in the realms of speculation. Sendroy and Hastings¹⁷ concluded that "we are

14 Pawlow. Im Laboratorium gemachte Beobachtungen über die Knochenforschung beim Hunde, Verhandl. d. gesellsch. Russ. Ärzte zu St. Petersburg **72** 314, 1904.

15 Whipple, G. H. The Origin and Significance of the Constituents of the Bile, *Physiol. Rev.* **2** 440 (July) 1922.

16 Seidel, H. Permanente Gallengiste und Osteoporose beim Menschen, *München med. Wchnschr.* **39** 2034, 1910.

17 Sendroy, J., Jr., and Hastings, A. B. Studies of the Solubility of Calcium Salts. III. The Solubility of Calcium Carbonate and Tertiary Calcium Phosphate under Various Conditions, *J. Biol. Chem.* **71** 797 (Feb.) 1927.

dealing with a complex system adjusted to function under normal conditions in such a manner as to furnish the organism with the optimum quantity of calcium wherever and whenever it is needed." In the main, the underlying mechanisms for the causation of the blood calcium deficiency and defective calcification seems to be closely related to growth and nutrition, and both are progressive from the time of the induction of jaundice. If there is a relative curtailment of calcium assimilation necessary for growth processes early in the period of jaundice, it is reasonable to assume that the organism is drawing on its resources in the bones, even though their endowment is small. It would be difficult to establish a sudden breaking point for absorption of calcium late in the period of jaundice on the basis of pathologic-anatomic grounds. The progressive lowering of calcium in the blood serum occurring at a time of marked growth of the bones is highly suggestive. We would, therefore, suggest that uncalcified bone is formed as the result of the production of new bone at a rate which exceeds the rapidity with which calcium phosphate is deposited, but that there occurs an actual but deficient deposition of lime salts into this increased bone matrix.

SUMMARY AND CONCLUSIONS

A fairly uniformly progressive calcium deficiency occurs in the blood serum of jaundiced puppies during the period of growth.

The progressive lowering of the blood calcium is attributed to the deposition of lime salts into an increased matrix rather than to a breaking point in the intestine resulting in progressive failure of calcium absorption.

The maintenance of normal calcium values in the early stages of jaundice may be due to mobilization, namely, bone lysis.

The roentgenograms disclose a marked degree of rarefaction sixty days after the induction of jaundice. This is manifested by cortical thinning, relatively wide medullary spaces and a lack of contrast generally. After twenty days of jaundice, significant changes in bone density or structure do not occur. One animal developed bilateral cysts in the bones.

The four intrinsic factors in the production of faulty calcification are small calcium storage, the presence of a disturbed metabolic condition unfavorable to osteogenesis, an intestinal factor in which the absence of some catalytic agent in bile may be most important, and production of bone which exceeds the rapidity with which lime salts are deposited.

The observations made in these experiments, together with such other evidence as we have, lend support to the idea that the extra-hepatic functions of bile are closely related to normal bone metabolism.

Book Reviews

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR,
VOL. XI, SURGERY, PART 1, GENERAL SURGERY, ORTHOPEDIC SURGERY, NEURO-
SURGERY Pp 1,300 with 600 illustrations Washington, D C Govern-
ment Printing Office, 1927

This volume is beautifully bound and printed, and the illustrations are lavishly scattered through the pages

As a historical work the book will be of great value While containing little that is original, every phase of war surgery is covered by a real expert, usually the one whose special studies form the basis of the present views Most of the material is slightly rewritten from former scattered publications, but it is well reorganized into a carefully knit unit and forms a clear record of the war experiences of a number of scientists

After two chapters on the material of war, effect of gunfire, etc., an enormous section on statistics follows, which is remarkable for its completeness Every war injury is tabulated and classified and page after page of tables show the mortality and morbidity and other details of various types of wounds and fractures

In the section on general surgery special praise is due to Yates for the clear and concise summary of the newer knowledge of dealing with wounds of the chest Much clinical and experimental work is cited, and this new field in surgery is thoroughly covered The lessening of the mortality from such wounds following the introduction of modern methods is striking

De Tarnowski's article on "Surgery at the Front" is also of great worth and could well serve as a guide in some future war to organize a medical service from the trenches to the base hospital

The section on orthopedic surgery is adequate but not of great interest on account of the fact that the war brought about but few changes in this type of work The mechanical aids to surgery, however, are well described and their use explained

Part 3, neurosurgery, is thorough and contains articles of Cushing, Frazer, Pollock and others In this field many additions to our knowledge were gained by intensive study and the section is therefore of great interest

The final chapter by Huber dealing with his experimental work on nerve regeneration is worthy of highest praise, as is the work of Pollock on peripheral injuries

A great section of the volume is taken up by the studies on wound shock and the methods of combating wound shock This work was largely done in collaboration with a number of physiologists Much of the experimental work was done hastily under the stress of active warfare and is perhaps rather inconclusive However, it is the vast experience of a great many surgeons as well catalogued in a symposium on this matter and it cannot fail to be of great value to further military surgeons Indeed, the whole book seems to be more of a history than a scientific contribution, and in this field it is doubtful if the object could have been any better achieved

TRABAJOS Y PUBLICACIONES—DE LA CLINICA By PROFESSOR PEDRO ESCUDERO
Price, \$12 Buenos Aires El Ateneo, 1925

This is the fourth volume of the collected publications of the Escudero Clinics, and serves to call attention to the enormous amount of high class scientific work being contributed in the schools of our sister republic

The work opens with a detailed report covering about 150 pages of eight cases of Ayerzas' disease, the syndrome given rise to by sclerosis of the pulmonary arteries The thoroughness and completeness with which these cases of "black cardiacs" were studied is commendable Every means known

to medical science was applied and the syndrome can now be stated to have been placed on a firm basis so that diagnosis should be made in every case. While many of the articles in the book are of this type, i. e., meticulously and carefully detailed case reports, they compare favorably with any that I have ever seen.

The article on hyperglycemia and that on gerodermia may be placed in this category.

Escudero himself, in a short report, presents a very interesting and new conception of the pathogenesis of Banti's disease. He believes that the primary lesion is a chronic perisplenitis. This perisplenitis by itself mechanically gives rise to aplastic anemia with leukemia and a mild nucleosis, and the enlargement of the spleen in turn brings about a hepatic sclerosis, thus completing the picture of Banti's disease. He has observed cases illustrating each stage of this condition and is rather convinced that syphilis is an element in its etiology. A good deal of the work is of a negative nature, but nevertheless is important.

A parental administration of casein is shown by Peco to have no effect on the hyperglycemia of diabetes.

Puchulu shows that the administration of insulin has little, if any, effect on the course of hyperthyroidism, and Izzo also shows that insulin has no effect on the course of tuberculosis of the lung, and that the treatment of tuberculous diabetes by insulin has no effect on tuberculosis.

The volume is lavishly illustrated with photographs, roentgenograms, electrocardiographs and other charts, and represents indeed a monumental work to be produced in one year.

MANUAL OF MATERIA MEDICA FOR MEDICAL STUDENTS. By E. Q. THORNTON. Price, \$4.50. Pp. 384. Philadelphia: Lea & Febiger, 1927.

This book of 384 pages is essentially a catalogue of drugs listed in the U. S. Pharmacopeia with a brief statement of origin and general character of the drugs. It is essentially an enlarged model of *Useful Drugs* (A. M. A.) and, as stated in the preface, does not attempt to present to the medical student a pharmacologic basis underlying clinical usage of the drugs. Such a book as this appears to be entirely uncalled for and would seem to have no place in the teaching of modern pharmacology and therapeutics to medical students.

OVERCOMING TUBERCULOSIS. AN ALMANAC OF RECOVERY. By GERALD B. WEBB, M.D., and CHARLES T. RYDER, M.D., Colorado School of Tuberculosis, Colorado Springs, Colo. Third edition, revised. Cloth. Price, \$2. Pp. 81, charts additional. New York: Paul B. Hoeber, Inc., 1927.

This is the third edition of the former work "Recovery Record, for Use in Tuberculosis," by the same authors. The title has been changed and certain minor changes and additions have been made. It is a valuable compendium for the tuberculous patient, and sufficient charts are appended to allow a daily record to be kept for over two years.

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